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(54) Title: STARCH-BASED CONTROLLED RELEASE COMPOSITIONS

(57) Abstract

This invention relates to controlled release compositions comprising (i) a matrix comprising starch having been processed under shear at temperatures of about 80 °C to about 240 °C in a closed volume wherein the water content of said matrix was maintained at about 5 % to about 45 % by weight based on the starch/water mix and (ii) an active ingredient, preferably a pharmaceutically active ingredient, wherein said matrix is in intimate contact with said active ingredient and wherein said matrix and pharmaceutically active ingredient are present in amounts sufficient to control the release of the pharmaceutically active ingredient in an effective dose.

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STARCH-BASED CONTROLLED RELEASE COMPOSITIONS

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention relates to controlled release therapeutic compositions which are capable of delivering their therapeutic active or agent over a predetermined period of time. These compositions may be used wherever controlled release is desired, i.e., in medicine, food, agriculture and the like. More particularly, this invention relates to sustained release compositions as well as those which require fast or moderate release periods of the active.

2. Description of Related Art

The convenience of administering a single dose of a medication which releases active ingredients in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized.

The advantages of a variety of sustained release dosage forms are well known. Among the most important advantages are: (1) increased contact time for the drug to allow for local activity in the stomach, intestine or other locus of activity; (2) increased and more efficient absorption for drugs which have specific absorption sites; (3) the ability to reduce the number of dosages per period of time; (4) employment of less total drug; (5) minimization or elimination of local and/or systemic side effects; (6) minimization of drug accumulation associated with chronic dosing; (7) improved efficiency

and safety of treatment; (8) reduced fluctuation of drug level; and (9) better patient compliance with overall disease management.

Additionally, many experts believe sustained release drug delivery has many important non-therapeutic ramifications as well, including a financial saving to the patient in terms of less lost work days, less hospitalization and fewer visits to the physician.

It is known that certain design parameters are critical to proper drug delivery. Typically, they are: (1) delivering the drug to the target tissue; (2) supplying the drug in the correct temporal pattern for a predetermined period of time; and (3) fabricating a delivery system that provides drug in the desired spatial and temporal pattern. Controlled or sustained release drug delivery systems are intended to manipulate these parameters to achieve the aforementioned advantages when compared to conventional pharmaceutical dosing. A typical drug concentration versus time profile for a conventional dosage form (A) and an idealized sustained drug delivery system (B) might look as shown in Figure 16.

The patent and scientific literature is replete with various sustained release (SR) methods and formulations. For common methods of obtaining SR systems, see Sustained and Controlled Release Drug Delivery Systems, Robinson, Joseph R., Ed., PP 138-171, 1978, Marcel Dekker, Inc. New York, NY. For example, it is known to fill polymeric capsules with a solid, liquid, suspension or gel containing a therapeutic agent which is slowly released by diffusion through the capsule walls. Heterogeneous matrices, for example compressed tablets, control the release of their therapeutic agents either by diffusion, erosion of the matrix or a combination of both. Other SR systems focus on the fabrication of laminates of polymeric material and therapeutic agent which are then

formed into a sandwich, relying on diffusion or er sion to control releas of the therapeutic agent. Liquid-Liquid encapsulations, whereby a liquid therapeutic agent is encapsulated in a viscous syrup-like solution of polymer, have also been known to be useful in controlling release of the therapeutic agent. Additionally, it is generally known that heterogeneous dispersions or solutions of therapeutic agents in water-swellable hydrogel matrices are useful in controlling the release of the agent by slow surface-to-center swelling of the matrix and subsequent diffusion of the agent from the water-swollen part of the matrix.

During dissolution of a controlled release matrix tablet, the dosage form generally remains as a non-disintegrating, slowly eroding entity from which the therapeutic agent leaches out, through a diffusion controlled process. Conventional SR formulations are generally designed to release their actives over an extended period of time, usually 8-24 hours. Conventional SR formulations use waxes or hydrophilic gums as the primary drug carriers to prolong the release of the active ingredients. In conventional wax matrix tablet formulations, the drug is dispersed in the wax matrix in the molten state. One disadvantage of this method, however, is that decomposition and/or crystalline transformation of the drug may occur, thereby rendering the drug less effective as a therapeutic agent. Additionally, because relatively large amounts of wax are necessary in such preparations, this may be undesirable from an overall therapeutic point of view. Conventional waxes and waxy materials used in pharmaceutical formulations are carnauba wax, spermaceti wax, candellila wax, cocoa butter, cetosteryl alcohol, beeswax, partially hydrogenated vegetable oils, ceresin, paraffin, myristyl alcohol, stearyl alcohol, cetylalcohol and stearic acid. They are generally used in amounts of about 10 to about 50% by weight of the total formulation.

Hydrophilic gums have also been known to be reasonably effective as SR carriers for both high-dose and low-dose drugs. However, because they tend to swell and form a gel upon contact with aqu us medium, they tend to entrap the drug substance and impede drug release more than desired, particularly in low dose formulations. Typical hydrophilic gums used as SR carrier materials are acacia, gelatin, tragacanth, veegum, xanthan gum, carboxymethyl cellulose (CMC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC). Generally these materials are present in amounts of about 10 to 50% by weight of the final formulation.

Starch USP (potato or corn) is commonly used as a component in conventional tablet or hard shell capsule formulations. It generally functions in conventional applications as a diluent or as a disintegrant in oral dosage forms. Starch paste is also often used as a binder in these products. Various modified starches, such as carboxymethyl starch currently marketed under the trade name Explotab or Primojel are used both in tablets and capsules as disintegrating agents. The literature discloses that native and modified starches are useful in promoting rapid release of drugs from solid oral dosage forms. Additionally, native starch has been used in some instances as a binder to produce granulations of active drug substances. More recently, pregelatinized starch has been reported as being useful as an SR matrix for theophylline formulations by Herman and Remon, "Modified Starches as Hydrophilic Matrices for Controlled Oral Delivery; III Evaluation of Sustained-Release Theophylline Formulations Based on Thermal Modified Starch Matrices in Dogs," in International Journal of Pharmaceutics, 63 (1990) 201-205. In sustained release applications several types of modified starch were mixed with anhydrous theophylline (60:40 W/W) as well as with silicon dioxide (Aerosil 200) and sodium benzoate. In prior papers, (International Journal of Pharmaceutics,

volumes 56, (1988) 145-153; 56 (1989) 51-63; and 56 (1989) 65-70) the authors discussed the use of both drum-drying and extrusion of native starch s to obtain partial or full pregelatinization. These articles conclude that high amylose starches, e.g. those containing 70% amylose such as Hylon VII (National Starch) do not produce good SR tablets because they do not form a sufficiently obstructive gel layer at the tablet surface, but rather progressively form a spongy layer as the tablet swells. This layer quickly erodes, resulting in a fast rather than sustained drug release. These references do suggest, however, that extrusion and drum-drying methods can be employed to produce sustained release theophylline formulations using starches containing 25% amylose.

One conclusion of the authors was that the thermal treatment of the starch, i.e. drum-dried versus extrusion, played only a minor role in sustained release performance. Another conclusion of the authors was that drum-drying of low amylose starch was useful in producing SR formulations when compared with formulations made from Theodur 300 (Astra-Nobelpharma, Brussel, Belgium). Theodur 300 is the trade name for a commercially available sustained release theophylline product. This system comprises theophylline coated onto sugar beads, which beads are then encapsulated with lipids, such as glyceryl monostearate, cetyl alcohol, beeswax, shellac and/or an acid resistant polymer such as cellulose acetate phthalate. The encapsulated beads are then compressed into a matrix containing the drug.

Pregelatinized starch is defined in the National Formulary XVII (1990) as starch which has been chemically and/or mechanically processed to rupture all or part of the granules in the presence of water and subsequently dried. Typically this is done by cooking and mixing an aqueous slurry of starch for a predetermined time until the granular structure of the starch is physically

distorted or partially broken apart. This does not result in any significant change in the molecular structure of the starch.

Extrusion cooking of food materials with starch has been differentiated from conventional plastic extrusion by various authors. For example, see P. Colonna, A. Buleon and C. Mercier, "Physically Modified Starches," in Starch: Properties and Potential, Ed., T. Galliard, John Wiley & Sons, New York, NY, 1987, where conservation of the macromolecular structure is said to be fundamental to the extrusion cooking process.

Other starches that have been used in the past in conjunction with active ingredients in drug delivery systems include Starch 1500, a pre-gelatinized starch marketed by Colorcon, Inc., and Merigel XX, marketed by Amylum, a Belgian Company.

The existing sustained release technologies generally involve relatively complicated formulations and manufacturing processes which are difficult and expensive to precisely control. For example, one well known SR delivery system, OROS, marketed by the Alza Corporation, involves laser drilling through a tablet to create a passage for the release of the drug from the tablet core. Other systems which use a variety of waxy materials and hydrophilic gums raise questions of the desirability of ingesting these materials. It is apparent, therefore, that there is a need for an inexpensive, easily controlled and relatively uncomplicated means of delivering actives.

As explained above, prior art systems have included starch for various purposes in pharmaceutical products. Most of these uses do not show sustained release properties and with few exceptions has starch demonstrated any particular advantages or benefits.

The instant invention overcomes the disadvantages of the prior art by offering a relatively simple and inexpensive means of obtaining controlled release through the use of a natural, biocompatable material which is obtainable through a renewable resource.

Recently, however, it has been disclosed in assignee's United States Patents 4,673,438 and 4,900,361 as well as EPO publication 327,505 (published August 9, 1989), that under certain conditions, starch can be rendered destructurized without degradation. This means that the granular structure has been substantially broken down. Depending on the parameters used to obtain overall destructurization, a variety of levels or degrees of destructurization can be reached. At each level, however, a substantial amount of the starch is in the molecularly dispersed form whereby the granular structure (starch granules) normally present in native or gelatinized starch is substantially destroyed, as evidenced by observation using conventional optical microscopy. The properties of destructurized starch are significantly different from those of pregelatinized starch and include the ability to be melted and reformed using standard extrusion techniques normally employed for thermoplastic polymers. Starch which has been destructurized in this manner can be said to be thermoplastic in nature.

Heretofore, destructurized starch has been used in injection molding applications, extrusion applications and combined with various polymers and other additives to make finished products. In particular injection molded capsules have been made from destructurized starch.

It has now been discovered that molecularly dispersed starch (MDS) can be effectively used as a novel controlled release matrix for a number of actives including pharmaceuticals, OTC medicaments, sweeteners, flavors, coloring agents and other ingestible materials

which, when controllably released, result in improved products. Additional uses, however, include materials which ar not intended for ingestion such as fertilizers, poisons, pesticides and other ch micals which when controllably released into the environment result in enhanced performance or other advantages.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 illustrates the dissolution profile of tacrine HCl tablets made from the inventive composition of Example 1 as compared to the conventional compositions of Examples 2 and 3.

Figure 2 illustrates the effect of different dissolution media on the inventive composition of Example 1.

Figure 3 graphically depicts the 24 hour release profile using both conventional USP recommended apparata, i.e. the paddle apparatus and the basket apparatus.

Figure 4 illustrates 24 hour release profiles of the inventive composition of Examples 4 and 5 wherein the lubricants magnesium stearate and glyceryl behenate are used. Also shown is the release profile for Example 1 which does not include lubricants.

Figure 5 graphically shows the 24 hour profile of several different dose strengths of tacrine HCl, per inventive tablet (Examples 1 and 6).

Figure 6 illustrates the effects of moisture level on the 24 release profiles of the inventive composition of Example 1.

Figure 7 is a dissolution graph of capsules containing gemfibrozil in the inventive matrix and a conventional corn starch carrier, respectively.

Figure 8 is a dissolution graph of capsules containing tacrine HCl and comparing the inventive matrix with a native corn starch carrier.

Figure 9 is a dissolution graph showing the results of using two different dissolution apparati.

Figure 10 is a dissolution graph of tacrine HCl as a function of the different levels of starch destructurization.

Figure 11 is a dissolution graph showing the effect of pancreatin USP in the media on the inventive matrix.

Figure 12 is a dissolution graph comparing the release profiles of the inventive matrix with commercially available pregelatinized starch.

Figure 13 is a dissolution graph showing the effect of the lubricant sodium benzoate on the inventive matrix as compared to pregelatinized starch.

Figure 14 is a dissolution graph showing the effect of the lubricant magnesium stearate on the inventive matrix as compared to pregelatinized starch.

Figure 15 is a dissolution graph comparing the SR profiles of the inventive matrix with pregelatinized starch.

Figure 16 is a graph showing a typical desired release profile for oral sustained release products.

Figure 17 is a graph showing the results of incorporating a carbonate salt excipient into a formulation comprising destructurized starch.

Figure 18 shows the dissolution rates of diphenhydramine in formulations containing different types of starch.

Figure 19 shows the dissolution rates of ibuprofin in formulations containing different types of starch.

Figure 20 shows the dissolution rates of phenytoin sodium in formulations containing different types of starch.

Figure 21 shows the dissolution rates of gemfibrozil in formulations containing different types of starch in a pH 7.5 buffer with enzymes.

Figure 22 shows the dissolution rates of gemfibrozil in formulations containing different types of starch in a pH 7.5 buffer.

Figure 23 shows the dissolution rates of gemfibrozil in formulations containing destructurized starch and differing amounts of gemfibrozil in a pH 7.5 buffer with enzymes.

Figure 24 shows the dissolution rates of gemfibrozil in formulations containing destructurized starch and differing amounts of gemfibrozil in a pH 7.5 buffer.

Figure 25 shows the dissolution rates of gemfibrozil in formulations containing destructurized starch and various amounts of sodium carbonate in a pH 7.5 buffer.

Figure 26 shows the dissolution rates of gemfibrozil in formulations containing destructurized starch and magnesium carbonate or sodium carbonate in pH 7.5 buffer with enzymes.

Figure 27 shows the dissolution rates of gemfibrozil in formulations containing destructurized starch and magn sium carbonate or sodium carbonate in pH 7.5 buffer.

SUMMARY OF THE INVENTION

The invention concerns the use of starch which has been processed under specific conditions in order to render it suitable as a sustain release (SR) or controlled release (CR) matrix when combined with therapeutic agents and other chemical entities which are intended to be controllably released. More particularly, the instant invention relates to controlled release pharmaceutical compositions comprising (i) a matrix comprising starch which has been processed under shear at temperatures of about 80°C to about 240°C in a closed volume wherein the water content of said starch is maintained at about 5% to about 45% by weight based on the starch/water mix and (ii) a pharmaceutically active ingredient, wherein said matrix is in intimate contact with said active ingredient and wherein said matrix and said pharmaceutically active ingredient are present in amounts sufficient to control the release of the pharmaceutically active ingredient in an effective dose. Starch which has been processed under these conditions has been found to be substantially free from intact starch granular structure and is said to be destructurized or in the molecularly dispersed state.

For purposes of this application the following definitions apply. The terms destructurized starch, molecularly dispersed starch (MDS) and thermoplastic starch will be used interchangeably. However, it should be recognized that the term "destructurized starch" may be broader in scope than "molecularly dispersed starch", although both can be processed using thermoplastic techniques. Without wishing to be bound to any one theory, molecularly dispersed starch is believed to be a

higher level within the category of destructurized starch.

Als useful in the instant invention are starch melts which may be used as controlled release matrices. Starch melts processed in the parameters set forth herein generally have a substantial disruption of the granular structure. Starch melts processed at the lower end of the processing parameters, can be considered an early or first level of destructurization. As the melt becomes more uniform, the disruption of the granular structure becomes even more evident, yielding a second level of destructurization. A third level of destructurization involves heating the melt above the glass transition temperature and melting point of the ingredients. At this level the melt is clearly a thermoplastic material. The last level of destructurized starch involves the formation of a molecularly dispersed starch. At this level, the melt has been heated to a high enough temperature for a sufficient time so that the specific endothermic transition analysis as represented by a differential scanning calorimetry curve indicates that a specific relatively narrow peak just prior to oxidation and thermal degradation has disappeared.

The terms "starch melt" or "molten starch" when used herein to describe the inventive compositions will mean starch which has been processed in accordance with the parameters given.

The term "active ingredient" will include, but not be limited to, pharmaceutically active ingredients, such as drugs, medicaments, therapeutic agents and other chemicals or materials useful in treatment of mammals, other animals, insects, fish and plants. In addition, this term will include non-ingestible materials and chemicals which are useful in, for example, agricultural applications, and ingestible materials for food applications and numerous other applications where the

active ingredient is to be released into the surrounding environment via the inventive matrix.

This invention also relates to a controlled release therapeutic composition comprising (i) a matrix of starch being substantially free of intact starch granules; and (ii) a therapeutic agent. The matrix can comprise destructurized starch and preferably molecularly dispersed starch. The inventive compositions can be made by forming an admixture of (i) starch which has been processed to obtain a melt, e.g. under shear in a closed volume at temperatures of about 80° to about 240°C, and preferably about 130°C to about 160°C, while maintaining the water content of the said matrix in the range of about 5% to about 45%, and preferably about 10% to about 25% by weight based on the total weight of the starch/water mix; and (ii) a pharmaceutical active. An alternative method of preparing the inventive compositions comprises mixing a therapeutic active with starch under sufficient conditions of temperature, shear and moisture to produce a controlled release composition.

U.S. Patent No. 4,673,438, which patent is incorporated herein by reference, discloses that natural starch (found in vegetable products) that contains a defined amount of water can be treated at an elevated temperature in a closed volume, and at elevated pressures, to form a melt. The process is conveniently carried out in an injection molding machine or extruder. The starch is fed through a hopper onto a rotating, reciprocating screw. The feed material moves along the screw toward the tip. During this process, the temperature of the material is increased by means of external heaters around the outside of the barrel and by the shearing action of the screw. Starting in the feed zone and continuing in the compression zone, the particulate starch feed becomes gradually molten. It is then conveyed through the metering zone, where homogenization of the starch melt occurs, and then

continues to the end of the screw. The molten material at the tip can then be treated further by injection molding or extrusion or any other known technique to treat th rmoplastic melts, to obtain shaped articles.

Using this process, it is believed that substantial destructurization of the starch occurs when the starch is heated above the glass transition temperature of the starch and the melting temperatures of its components. As a consequence, a melting and substantial disordering of the molecular structure of the starch granules takes place, so that a high level destructurized starch is obtained.

In the present invention it is preferred that the destructurized starch be heated to a high enough temperature and for a time sufficient so that the specific endothermic transition analysis as represented by a differential scanning calorimetry (DSC) curve indicates that a specific relatively narrow peak just prior to oxidation and thermal degradation has disappeared, as described in copending U.S. patent Application Serial Number 278,116, which is incorporated herein by reference.

Copending U.S. Application Serial No. 539,846, also incorporated herein by reference, describes the combination of a variety of hydrophobic and hydrophilic plastic materials with destructurized starch to form dimensionally stable articles. Unlike starch, conventional thermoplastic materials are hydrophobic, substantially water-insoluble polymers that are conventionally processed in the absence of water and volatile materials. Starch, on the other hand, normally forms a melt in the presence of water but decomposes at elevated temperature, i.e., around 240°C. Therefore, it was unexpected, in view of its hydrophilic nature and chemical structure that a starch melt would be useful in c mbination with other hydrophobic, substantially

water-insoluble polymeric materials. These combinations of d structurized starch with various thermoplastic polymers disclosed in pending U.S. Application Serial No. 539,846 are also found to be useful in the inventive SR compositions as further described herein.

Although the controlled release mechanism of the starch melt matrices used in the inventive compositions is not completely understood, it is hypothesized that the formation of the melt allows for better compressibility and possibly denser tablet formation. The increased compressibility and/or density of these matrices may contribute to the SR action of the composition.

Starches which are considered useful in the instant invention include starches obtained from natural sources as well as chemically and physically modified starches. Starch derived from corn, waxy maize, wheat, potato, rice, rye, oats, tapioca, pea, and the like are examples of natural starches which are useful in the instant invention. Starches which are genetically or biologically modified are also useful.

Both water-soluble and water-insoluble drugs have been found to be useful in the delivery systems covered by the invention. For purposes of this application, the terms water-soluble and water-insoluble drug will have the following definitions. Water-soluble drug will mean that up to 30 parts of solvent are required to completely dissolve 1 part of drug. The term water-insoluble drug will mean greater than 30 parts of solvent are required to dissolve 1 part of the drug. For further discussion of these terms, see USP XXII, page 1807 incorporated herein by reference. The compositions can be used to obtain specific controlled release profiles, combining aspects of immediate release, intermediate release, and sustained release in one formulation. For example drugs falling into the following therapeutic categories are representative of those that could be used in combination

with the novel delivery matrix. These drugs include, but are not limited to, ACE inhibitors; anti-anginal drugs; anti-arrhythmias; anti-asthmatic; anti-ch lester lemic; anti-convulsants; anti-depressants; anti-diarrhea preparations; anti-histamines; anti-hypertensive drugs; anti-infectives; anti-inflamatory agents; anti-lipid agents; anti-manics; anti-nauseants; anti-stroke agents; anti-thyroid preparations; anti-tumor drugs; anti-tussives; anti-uricemic drugs; anti-viral agents; acne drugs; alkaloids; amino acid preparations; anabolic drugs; analgesics; anesthetics; antacids; antiarthritics; antibiotics; anticoagulants; antiemetics; antiobesity drugs; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotic drugs; anxiolytic agents; appetite stimulants; appetite suppressants; beta blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholycistekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; erythropoietic drugs; expectorants; fertility agents; fungicides; gastro-intestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypnotics; hypoglycemic agents; laxatives; migraine treatments; mineral supplements; mucolytics; narcotics; neuroleptics; neuromuscular drugs; NSAIDS; nutritional additives; peripheral vaso-dilators; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vaso-constrictors; vaso-dilators; vertigo agents; vitamins; and wound healing agents and mixtures thereof.

A variety of different dosage forms, explained more fully herein, have been found to be useful and can be chosen to fit a specific application. Mixtures of appropriate drugs are also contemplated.

Processes which are useful in fabricating both the dosage form and the compositions per se of the instant invention, include any of those well known to the art.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the invention comprise a ratio of matrix to active ingredient sufficient to controllably release the active at an effective or desired rate and amount. In the case of pharmaceutically active ingredients, this ratio may vary considerably, depending on the properties of the drugs involved, specific dosage form, process of preparation of the overall composition, the addition of various additives, as well as other factors which may dictate a useful therapeutic ratio. For example, in the case of procaterol, the amount of drug used may be as little as .05 mg per 100 mg tablet. This represents a ratio of about 2000 to 1 of matrix to drug. On the other hand, in the case of procainanide as much as 1000 mg per 1300 mg tablet may be used, representing a ratio of 0.3 to 1 of matrix to drug. Another example of a high dose drug is gemfibrozil, which may be as much as 600 mg of drug in a 1 gram tablet, representing a ratio of about 1.0 to about 1.5. In general, the ratio of matrix to drug may range from about 5 to 95 to about 99.999 to 0.001, depending on the factors discussed above. Preferably the ratio of matrix to drug is about 1 to 9 to about 9 to 1. In practice, any ratio of matrix to pharmaceutically active ingredient which controls the release of the active at an effective rate and dose for the intended purpose is useful.

As previously stated, those starches useful in the matrix may be obtained from natural, modified or genetically engineered starches. The starch may be destructurized prior to admixture with the active ingredient or, if the active ingredient is sufficiently stable, the active ingredient may be added to the starch prior to destructurization and subsequently passed

through the destructurization process. The inventive compositions may us all of ne type of starch or may us a combination of different starches to achieve differ nt release properties. Starch processing parameters vary within the aforesaid ranges of starch, water content, shear and temperature, as is known in the art. It should be noted, moreover, that it has recently been discovered that certain polyols, such as sorbitol, mannitol, xylitol and the like, may be substituted for or added in addition to some or all of the water in the destructurization of the starch. Although aqueous starch systems are preferred in achieving destructurization, other ingredients which may be found to be useful in achieving this end are contemplated.

The destructurized starch may also be essentially free of bridged phosphate groups, which as disclosed in U.S. Patent 4,900,361, incorporated herein by reference, produces molded articles which have substantially less defects than those destructurized starches where the phosphate groups are bridged. This is accomplished by a process which substantially removes multivalent bridging ions and the free electrolytes associated therewith.

Due to the unique physical and chemical properties of the inventive matrix, it may be combined with a wide variety of pharmaceutically active ingredients having a wide range of chemical and therapeutic characteristics. For example, both highly water soluble active and highly water-insoluble actives have been found to be useful. More specifically, non-limiting specific examples of pharmaceutically acceptable actives can be chosen from the list which follows. Mixtures of these drugs and their salts used for appropriate therapies are also contemplated. Pharmaceutically active compounds include, but are not limited to, acetaminophen; acetic acid; acetylsalicilic acid and its buffered form; albuterol and its sulfate; alcohol; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate, hydroxide; alprozolam; amino

acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; aneth le; ascorbic acid; aspartame; atenolol; bacitracin; balsam peru; beclomethasone dipropionate; benz cain ; benzoic acid; benzophenones; benzoyl peroxide; biotin; bisacodyl; bornyl acetate; bromopheniramine maleate; buspirone; caffeine; calamine; calcium, calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalexin; cetylalcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine maleate; cholestyramine resin; choline bitartrate; cimetidine hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; cocoa butter; cod liver oil; codeine and codeine phosphate; clonidine and its hydrochloride salt; clorfibrate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; danthron; dexbrompheniranime maleate; dextromethorphan hydrobromide; diazapam; dibucaine; diclofenac sodium; digoxin; diltiazem; dimethicone; dioxybenzone; diphenhydramine citrate; diphenhydramine hydrochloride; docusate calicum, potassium and sodium; doxycycline hyclate; doxylamine succinate; efaroxan; enalapril; enoxacin; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; ferrous fumarate, gluconate and sulfate; folic acid; fosphenytoin; fluoxetine HCl; furosemide; gabapentan; gemfibrozil; glipizide; glycerin; glyceryl stearate; griseofulvin; guaifenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone bitartrate; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; ibuprofen; indomethacan; inositol; iodine; ipecac; iron; isoxicam; ketamine; koalin; lactic acid; lanolin; lecithin; lidocaine and its hydrochloride salt; lifinopril; liotrix; lovastatin; magnesium carbonate, hydroxide, salicylate, trisilocate; mefenamic acid; meclofenanic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate;

menthol; meperidine hydrochloride; metaproterenol sulfate; methyldopa; methyl nicotinate; methyl salicylate; methylcellulos ; methsuximid ; metr midazole and its hydrochloride; metoprolol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its sodium salt; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nitroglycerin; nonoxynol-9; norethindone and its acetate; nystatin; octoxynol; octoxynol 9; octyl dimethyl PABA; octyl methoxycinnamate; omega-3 polyunsaturated fatty acids; omeprazole; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate 0; paramethadione; pentastatin; peppermint oil; pentaerythriol tetranitrate; pentobarbital sodium; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine hydrochloride; phenylpropanolamine and its hydrochloride salt; phenytoin; phenelzine sulfate; pirmenol; piroxicam; polymycin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; propoxyphene and its HCl salt; propoxyphene napsylate; pramiracetin; pramoxine and its hydrochloride salt; propronolol HCl; pseudephedrine hydrochloride and sulfate; pyridoxine; quinapril; quinidine qluconate; quinestrol; ralitoline; ranitadine; resorcinol; riboflavin; salicylic acid; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate and fluoride; sodium monofluorophosphate; sulfanethoxazole; sulfur; tacrine and its HCl salt; theophylline; terfenidine; thyroid; thioperidone; trimethrexate; triazolam; timolol maleate; tretinoin; tetracycline hydrochloride; tolnaftate; triclosan; triprolidine hydrochloride; undecylenic acid; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B_1, B_2, B_6, B_{12}, E, K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; and zinc undecylenate.

One particular group of compounds useful in this invention are CCK-B antagonists. These compounds are

described in copending U.S. Serial Numbers 629,809 filed 12/19/90, 576,308 filed 8/31/90, 576,628 filed 8/31/90, 576,296 filed 8/31/90, 576,315 filed 8/31/90, 576,024 filed 8/31/90 and 576,297 filed 8/31/90, all of which ar herein incorporated by reference. One especially useful compound is [R-(R*,R*)]-4-[[2-[[3-(1H-indol-3-Yl)-2-methyl-1-oxo-2-[-[(tricyclo [3.3.1.1^{3,7}] dec-2-yloxy)- carbonyl] amino] propyl]- amino]-1- phenylethyl]- amino]-4- oxobutanoic acid.

Additionally, the inventive compositions can be used in conjunction with ion exchange resins, cosmetic preparations, comestibles such as gum and confectionery products, as well as food products.

With respect to various gum, confectionery and snack food applications, the controlled release compositions of the instant invention may be used to produce aerated confectioneries such as ropes, rolls, films, chewable candies, hard candies, puffed snacks as well as aerated chewing gums. The aeration techniques used may be produced by foaming techniques. The inventive compositions can also be used in encapsulation applications for flavors, sweeteners, spices and other ingredients used in the food art. Our particularly novel usage relates to the formation of potato chips and other fried starch-based foods using extrusion or injection molding techniques, thereby creating a healthier product. Bioadhesive formulations for use in snacks, mints and chewing gum are also contemplated. In addition, the inventive compositions may be formed into dry or liquid soup formulations. Cereals may also be blended or coated with the inventive compositions. Co-extruded products are also possible. The inventive compositions can also be used in a variety of food formulas to modify the texture and plasticization as well as to produce better compatibility with other ingredients.

In th case of chewing gums, the inventive compositions may be employed to extend the flavor and/or sweetness of the gum. In general, the inventiv c mpositions may be used in amounts of up to about 85% by weight of the final chewing gum composition. Preferred amounts are about 15 to about 70% by weight and most preferably about 20 to about 50% by weight. The gum base may be any water-insoluble gum base well known in the art. Illustrative examples of suitable polymers in gum bases include both natural and synthetic elastomers and rubbers. The inventive compositions, however, may lend theirself to formulating biodegradable gum bases per se.

Gum base compositions may contain elastomer solvents to aid in softening the rubber component. Such elastomer solvents may comprise any of the conventional solvents such as wood rosins and terpene resins. The solvent may be employed in an amount ranging from about 10% to about 75% and preferably about 45% to about 70% by weight of the gum base.

The chewing gum composition may include the conventional additives of flavoring agents, coloring agents, plasticizing agents, softeners and other ingredients. Preferably, these ingredients may be used in amounts of about 10% to about 30% by weight of the final chewing gum.

A variety of sweeteners are useful including sucrose, amino acid-based sweeteners, chloro derivatives of sucrose, dihydroflavinol, hydroxyguaiacol esters, L-amino dicarboxylic acid gem-diamines, L-aminodicarboxylic acid, aminoalkenoic acid ester amides, dipeptide sweeteners, glycyrrhizin, saccharin and its salts, acesulfame salts, cyclamates, steviosides, talin, dihydrochalcone compounds and mixtures thereof.

The sweeteners which may be released from the matrix may be used in amounts necessary to impart sweetness and

preferably in am unts of about 1% to about 30% by weight of the matrix. Aspartame, saccharin, sucralose, acesulfame and its salts are the preferred sweeteners and may be used in amounts of ab ut 1% to about 50% and about 1% to 50%, respectively, by weight of the matrix. The preferred amounts of these sweeteners are about 2 to about 25%, most preferably about 5 to about 15%.

Suitable flavorings including both natural and artificial flavors, and mints such as peppermint, menthol, artificial vanilla, cinnamon, various fruit flavors, both individual and mixed, and the like are contemplated. The flavorings are generally utilized in amounts that will vary depending upon the individual flavor and may, for example, range in amounts of about 0.5% to about 3% by weight of the final chewing gum composition.

A variety of additives can be incorporated into the inventive compositions for their intended functions. Examples of classes of additives include excipients, lubricants, buffering agents, disintegrating agents, stabilizers, foaming agents, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, antiadherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added before heating the starch to form the melt or after this step.

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, rape seed proteins, blood proteins, egg proteins, acrylated proteins; water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, gum arabic

and related gums (gum ghatti, gum karaya, gum tragacanth), pectin; water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxpropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as: cellulose acetate phthalate (CAP), Hydroxypropylmethylcellulose (HPMCP); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkalimetal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVP/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized, if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount preferably within the range of up to about 80%, preferably about 3 to 50% and more preferably within the range of 3% to 20% based on the weight of all components.

Further additives may be inorganic fillers, such as the oxides of magnesium, aluminum, silicon, titanium, etc. preferably in a concentration range of about 0.02 to about 3% by weight and preferably about 0.02 to about 1% based on the weight of all components.

Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols; organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate; propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5 to about 15%, and preferably ranging from about 0.5 to about 5% based on the weight of all the components.

Examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

There may further be added compounds to improve the flow properties of the starch material such as animal or vegetable fats, preferably in their hydrogenated form, especially those which are solid at room temperature. These fats preferably have a melting point of 50°C or higher. Preferred are triglycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}- fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantaegously added alone or together with mono- and/or diglycerides or phosphatides, especially lecithin. The mono- and diglycerides are preferably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}- fatty acids.

The total amounts used of the fats, mono-, diglycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5 to about 2% by weight of the total composition.

It is further useful to add silicon di xide or titanium dioxide in a concentration of about 0.02 to about 1% by weight of the total c mposition. These c mpounds act as texturizing agents.

Excipients may generally include croscarmellose sodium, pregelatinized starch, sodium starch glycolate, unmodified starch and crospovidone. These excipients are commonly referred to as disintegrants because they promote disintegration of the device and consequently rapid disintegration of the active ingredient from the dosage form. One preferred class of excipients is carbonate salts. These salts include, but are not limited to, sodium carbonate, sodium bicarbonate, calcium carbonate and magnesium carbonate. These excipients may be combined with the active ingredient in any form, e.g., by compression, molding or pelletizing. In one preferred embodiment of the invention having gemfibrozil as the active ingredient, the preferred excipient for rapid release is sodium carbonate.

These additives are to be used in amounts sufficient to achieve their intended purpose. Generally, the combination of certain of these additives will alter the overall release profile of the active ingredient and can be used to modify, i.e. impede or accelerate the release.

Useful dosage forms include without limitation oral forms such as tablets, capsules, beads, granules, aggregates, syrups, powders, gels, solids, semi-solids, suspensions and liquids. Injectable forms, lotions, transdermal delivery systems including patches, implantable forms or devices, aerosols or nasal mists, suppositories, salves and ointments are also useful.

Known pharmaceutical coatings such as enteric coatings as well as coatings for ease of swallowing, masking of unpleasant tastes and the like are useful in the instant invention.

Dosage forms of the present invention may be combined to achieve desired results. For example, a capsule may be comprised of and/or contain the inventive controlled released composition. The capsule may contain, for example, a granulate of the inventive composition. The actives in the capsule walls may be the same as or different from those inside the capsule cavity.

A variety of processing techniques known to those in the pharmaceutical art can be used to fabricate the dosage forms and composition forms. Compression of wet or dry granulations and mixtures is useful for tablet formation. Injection molding may be used to form capsules, tablets and other shapes such as suppositories, dipsticks and implantable devices. Filming, thermoforming, blow molding, extrusion, coextrusion and other known thermoplastic processing techniques can be employed. Cast molding into sheets and bars are also effective fabrication techniques.

The following in vitro examples are given to illustrate certain embodiments of the invention, but are not intended in any way to be limiting of the effective scope or spirit of the invention as described and claimed. All percentages are in percent by weight of the total composition unless otherwise indicated. Unless otherwise indicated, all tableted compositions were compressed into 3/8" flat-faced round tablets at 5000 psi using a conventional tabletting press. The tablets were then subject to dissolution tests in accordance with XXII USP test method #2. The dissolution tests were conducted by placing the test dosage units (tablets) in 900 ml of 0.1N hydrochloric acid as the dissolution medium and using a USP #2 apparatus (rotating paddle) at 50 rpm. Unless otherwise indicated, all examples use the following molecularly dispersed starch (MDS) pelletized composition:

EXAMPLES

EXAMPLE 1

Table I

MDS Composition

Component	% W/W
Potato starch	81.00
Hydrogenated triglyceride	1.00
Soya lecithin	0.50
Titanium dioxide	0.50
Water	17.00

Native potato starch having a water content of about 15-20% was fed into a twin extruder along with the other components listed above. The extruder barrel temperature profile was 80°/160°/120°C and the screw speed was set at 75 rpms. The residence time in the barrel was approximately 50-150 seconds. The teachings of United States Patent 4,673,438 were followed to produce a molecular dispersed starch melt. Material expelled from the extruder was cut into pellets and cooled. The pellets were shown to be readily meltable and reformable by extrusion, without loss of thermoplastic properties. When the pellets were observed under standard optical microscopy techniques, substantially all granular structure had been destroyed, giving the optical appearance of a relatively homogenous mixture or blend.

The pellets were then cryogenically milled into a powder to facilitate compression into a tablet. Due to the high hygroscopicity of the MDS, milling to fine uniform particulates is difficult, as the material is usually soft and rubbery, depending on the water content. Freezing the pellets prior to milling with liquid nitrogen or dry ice first allows for uniform communition. Subsequent to communition, the liquid nitrogen or dry ice are evaporated under controlled conditions to retain moisture in the sample. The particle mesh size has not

been found to be critical and will vary depending on the particular application and/or starch employed. Generally, for pharmaceutical applicati ns, U.S. mesh sizes of about 20 to about 100 are used, corresponding to micron size ranges of about 850 to about 150 respectively.

The milled MDS composition was then intimately dry mixed with each of the following compositions containing the highly water-soluble drug tacrine hydrochloride (9-Amino-1,2,3,4-tetrahydroacridine). In vitro dissolution tests (USP method) were then conducted to determine SR profiles. The figures graphically show the results of these tests.

EXAMPLE 2

Component	mg/tablet
Tacrine HCl	12.8
MDS (Table I)	287.2
Total	300.0

The dissolution results of this example are shown in Figures 1-3, 5, and 6.

As shown in Figure 1, the use of MDS as a delivery matrix for the water soluble drug tacrine HCl, provides an in vitro sustained release profile up to 24 hours. This is in comparison to the conventional compressed tablet composition which demonstrates an immediate high release of drug with complete release occurring within about 4 hours. As previously mentioned, Example 3 (conventional) is identical in components to Example 2 (inventive) except that instead of using MDS as the matrix, ordinary commercially available native starch is used. This demonstrates the SR effect MDS has on the drug composition.

Dissolution studies are conducted using three different media recommended by USP for evaluating oral

solid dosage forms: Distilled water; 0.1N hydrochloric acid; and 0.05M pH 7.5 phosphate buffer. As graphically shown in Figure 2, the SR profile ver 24 h urs is nearly identical irrespective of the media.

As seen from the graph in Figure 3, both apparata give similar 24 hour SR profiles for the inventive composition in Example 1.

Four MDS compositions were prepared as in Table I except that for each of these compositions, the water content of the composition was 17.7%, 15.8%, 10.8% and 5% respectively. While those compositions with 17.7% gave excellent sustained release profiles, those matrices with lower water contents showed lower sustained release characteristics (Figure 6). It must be emphasized, however, that more rapid release of active due to lower moisture contents of the MDS composition can be controlled through the use of other additives, as well as through other processing and fabrication techniques.

EXAMPLE 3

An identical set of components used to prepare the matrix in Table I was also used to provide a dry mixture without processing of the starch to produce MDS. This example is intended to show the comparative release properties of conventional tableted starch as compared to the instant invention. This composition is used in the following example and is denoted herein as a conventional starch mixture (CSM).

Component	mg/tablet
Tacrine HCl	12.8
CSM	287.2
Total	300.0

The results of dissolution tests are graphically shown in Figure 1 as having very little SR properties.

EXAMPLE 4

This example employs native, commercially available potato starch "as is" without further proc ssing, as the formulation matrix. This composition is similar to Example 3, except it does not have the other additives contained in CSM.

Component	mg/tablet
Tacrine HCl	12.8
Potato starch	287.2
Total	300.0

As evidenced by Figure 1, virtually no SR properties are obtained using this formulation.

EXAMPLE 5

The dissolution results of examples 5 and 6 are shown graphically in Figure 5. Magnesium stearate, a conventional tabletting lubricant, is combined with the MDS composition described in Table I.

Component	mg/tablet
Tacrine HCl	12.8
MDS (Table I)	285.7
Magnesium Stearate	1.5
Total	300.0

EXAMPLE 6

This example substitutes glyceryl behenate NF a lubricant in place of magnesium stearate of Example 5.

Component	mg/tablet
Tacrine HCl	12.8
MDS (Table I)	284.2
glyceryl behenate	3.0
Total	300.0

As depicted in the graphs of Figures 4 and 5, all the release profiles virtually match each other, suggesting that for direct compression tablets formed in the conventional manner described above, lubricants do not appear to affect the release profile of the inventive composition with a highly water soluble drug such as tacrine HCl.

EXAMPLE 7

This example illustrates the use of MDS as a matrix for vraious doses of the drug tacrine HCl. (See Figure 5)

Component	mg/tablet				
Tacrine HCl	51.8	51.8	51.8	51.8	51.8
MDS (Table I)	249.2	168.2	128.2	88.2	58.2
Mg Stearate	1.5	1.1	0.9	0.7	0.55
Total	302.5	221.1	180.9	140.7	110.55

As previously discussed, one parameter which is known to affect release properties of a drug composition is the relative proportion of drug to matrix. Generally, it is expected that the higher the drug:matrix ratio, the less sustained release due to the smaller proportion of matrix available to erode and thereby control diffusion and release of the drug.

EXAMPLE 8

The purpose of this example is to obtain a relatively fast release composition. The MDS composition of Table 1 was used in this example as the matrix for a drug composition for the highly water-insoluble drug, gemfibrozil. This composition was incorporated in a dry mixed form into a standard, commercially available gelatin capsule (No. 0 capsule).

Component	mg/tablet
Gemfibrozil	300.0
polysorbate 80 on Silica (surfactant)	10.0
MDS (Table I)	150.0
Total	460.0

The capsules containing this formulation were subjected to USP dissolution tests and the results displayed in Figure 7. Figure 7 shows the dissolution release over 60 minutes indicating a relatively fast release.

EXAMPLE 9

The following composition was prepared and incorporated into No. 0 gelatin capsules in the same manner as in Example 8.

Component	mg/tablet
Tacrine HCl	300.0
polysorbate 80 on Silica (surfactant)	10.0
MDS (Table I)	150.0
Total	460.0

Figure 8 illustrates the immediate release profile of capsules containing this composition.

EXAMPLE 10

The following composition was dry mixed and compressed into tablets in accordance with the procedure used in Example 2.

Component	mg/tablet
Hydrochlorothiazide	25.0
MDS (Table I)	275.0
Total	300.0

The 3/8" flat-faced, round tablets were then exposed to USP dissolution tests (0.IN HCl; 37°C) in both basket and paddle type apparata. The 24 hour sustained release profiles are shown in Figure 10. Hydrochlorothiazide is a relatively water-insoluble drug. The inventive MDS matrix of Table I, allows for uniform sustained release characteristics in vitro.

EXAMPLE 11

This example is intended to demonstrate further the improved sustained release properties the inventive starch melt, destructurized starch and MDS matrices have over prior art compositions using gelatinized starch. As previously described herein, MDS (molecularly dispersed starch) is formed under specific conditions of shear, temperature and water content, all of which occur in a closed volume. These parameters can be adjusted within the ranges of for example, about 80°C to about 240°C and preferably about 110°C to about 170°C; about 5% to about 45% water and with sufficient shear (screw speed, screw geometry and barrel length) for a time long enough to destructurize or substantially destroy the granular structure of the starch. The choice of these parameters can product different "levels" or "degrees" of destructurization. The different degrees of destructurization can be measured by various methods. One such method, for example, is to measure the remaining amount of granular structure contained in the destructurized starch. This can be determined by known microscopic methods. Gelatinized starch, on the other hand, is often cooked at various temperatures ranging from 55°C to 75°C and may be agitated or mixed using conventional mixing equipment. The r sultant product,

however cannot be said to be a melt or to be in the destructurized or molecularly dispersed form. This can b determined under standard optical microscopy techniques.

Tablets (300 mg) comprising a matrix of 287.2 mg of starch which has been subjected to various processing temperatures and shear during extrusion were fabricated using direct compression. Dissolution tests, as graphically illustrated in Figure 10 demonstrates the effect of temperature and shear on release. As the graph shows, processing at temperatures of 100°C to 160°C yield matrices which released the water-soluble drug tacrine HCl in substantially the same rates over a 24 hour period. This is to be compared with the starch matrix processed at 70°C, which exhibited sustained release action only over a six hour period.

EXAMPLE 12

This example uses the pancreatin USP to simulate intestinal fluid and demonstrates the effect of this enzyme on MDS matrices. MDS was prepared at 160°C and 300 mg tablets were compressed comprising 287.2 mg MDS and 12.8 mg of tacrine HCl. The tablets were then subjected to dissolution media having a pH of 7.5 and containing 10 g/L pancreatin. Identical test tablets were also run in standard HCl media (pH 1.2) as a comparison. The results, shown in Figure 11, demonstrate that the sustained release action of MDS matrices is reduced but still effective in simulated intestinal fluid. Further sustained release can be obtained through various additives which slow the degradation of the starch by pancreatin.

EXAMPLE 13

The MDS composition in Table 1 is duplicated using wheat starch and corn starch in place of potato starch.

The MDS composition is then combined with the following wat r-solubl therapeutic agents in the amounts as shown.

I.	Component	mg/tablet
	Wheat MDS	287.2
	Tacrine HCl	12.8
	Total	300.0

II.	Component	mg/tablet
	Corn MDS	250.0
	diphenhydramine HCl	50.0
	Total	300.0

In addition to tablets, powders and granules are formed from these compositions. The granulations are then put into standard capsules as well as compressed into tablets. Injection molded capsules are also fabricated from the granules.

EXAMPLE 14

This example demonstrates the effect of the matrix to drug ratio upon the release profile over a 24 hour period. The following components are formulated using MDS and water-soluble drugs.

Component	mg/tablet (range)
pseudephedrine HCl	30-240
chlorpeniramine maleate	2-24
Total	100-1000

EXAMPLE 15

The experiments in example 13 are repeated, this time substituting the following water-insoluble drugs for the soluble drugs.

Component	mg/tablet (range)
MDS	20-80
G mfibrozil	80-20
Total	100

EXAMPLE 16

A water-soluble suppository dosage form having the following composition is made:

Component	mg/suppository
MDS	35
Polyethylene glycol 4000	700
Polyethylene glycol 400	1060
Phenylephrine HCl	5
Total	2500

The components are mixed in a heated jacketed bottle and transferred to molds to cool.

EXAMPLE 17

The granulations of Example 13 are coated with one of the following encapsulating materials selected from ethylcellulose, methylmethacrylate copolymers, and cellulose acetate. The granulations are then incorporated both in tablets and capsules.

EXAMPLE 18

The following composition is prepared in the form of an injection molded or foamed suppository for vaginal application:

Component	mg/suppository
MDS	780
Clotrimazole	200
Talc	20
Total	1000

The components are combined in an extruder or injection molding machine. If an extruder is used, a foamed product is produced. The foamed product is designed for immediate release.

EXAMPLE 19

Commercially available pregelatinized starch matrices (National Starch 1500) were prepared. Comparative dissolution studies are run using tablets prepared identically to those of Example 2. The results, graphically shown in Figures 12, demonstrate the improved SR profiles obtained by destructurized starch matrices when compared to pregelatinized matrices.

EXAMPLE 20

The data given by Herman and Remon, in International Journal of Pharmaceutics, 63 (1990) were plotted in Figure 13 against actual in vitro data obtained using the inventive MDS matrix (160°C) for the same drug, theophylline. The lubricant sodium benzoate is incorporated. Tablets (300 mg) are compressed as discussed above and dissolution tests run in water. The results clearly indicate improved sustained release.

EXAMPLE 21

As in Example 20, data given in the Remon article was plotted against actual in vitro data obtained using the inventive MDS matrix (160°C). Magnesium stearate is used in place of sodium benzoate. The results of the dissolution tests (Figure 14) clearly show improved SR properties over 24 hours.

EXAMPLE 22

As in Example 20, data given in the Remon article was plotted (Figure 15) against actual in vitro data

obtained from dissolution tests of 300 mg tablets containing theophylline and MDS. No lubricant is incorporated into the inventive composition. Improved SR results are demonstrated by the inventive c mposition.

EXAMPLE 23

The following composition is prepared as a suspension:

Component	gms
MDS	5.0
Xanthan gum	0.025
mg hydroxide	8.0
Al hydroxide	8.0
Sorbitol (70% soln)	5.0
Glycerin	1.0
Methyl paraben	0.25
Peppermint oil	0.1
Water	q.s. 100 ml

EXAMPLE 24

The following composition is prepared in the form of a suppository designed to release the therapeutic active via melting.

Component	mg/suppository
Cocoa Butter NF	620
Witepsol suppository base	1000
MDS	700
Phenylephrine HCl	5
Total	2325

EXAMPLE 25

The following composition is prepared in the form of an ointment.

Component	g/Kg
Petrolatum	680
Mineral Oil	200
Wax	50
MDS	65
Phenylephrine HCl	2.5
Tween 20	2.5

The composition was mixed in a jacketed kettle at 80-90°C and allowed to cool to form the ointment.

EXAMPLE 26

A formulation comprising destructurized starch and an excipient to promote erosion and a control formulation were prepared as follows:

	mg/tablet	
Diphenhydramine HCl	25.00	25.00
Destructurized Starch	221.25	158.75
Magnesium Carbonate	-	62.50
Magnesium Stearate	2.50	2.50
Cab-O-Sil	1.25	1.25
Total	250.00	250.00

All the components except magnesium Stearate were dry blended by serial dilution. The lubricant was added and the mixture was compressed into a 3/8" tablet on a carver press at 5000 psi. The serial dissolution was carried out in a 2 paddle USP apparatus at 100 rpm, and at 37 degrees C. with 900 mL of 0.1 N HCl serving as the dissolution medium. The dissolution profiles fo the two formulations are shown in Figure 17.

EXAMPLE 27

Formulations were prepared having the following compositions:

(mg/tablet)

Diphenhydramine HCl	25.00	25.00	25.00	25.00
Dest. Starch	221.25	-	-	-
Merigel XX	-	221.25	-	-
Starch 1500	-	-	221.25	-
Potato Starch	-	-	-	221.25
Mg Stearate	2.50	2.50	2.50	2.50
Cab-O-Sil	1.25	1.25	1.25	1.25
Total	250.00	250.00	250.00	250.00

The formulations were prepared by mixing Cab-O-Sil with the active ingredient in a suitable blender. Destructurized starch that had been screened through No. 30 screen mesh to remove aggregates, or a comparison starch, as appropriate, was then added and the components were then blended for 15 minutes in a high shear mixer. Finally, the lubricant was added, and the entire mixture was blended for 3 minutes without using an intensifier bar. The release profiles of the formulations are shown in Figure 18.

EXAMPLE 28

Formulations were prepared having the following compositions:

(mg/tablet)

Ibuprofen	200.0	200.0	200.0	200.0
Dest. Starch	292.5	-	-	-
Merigel XX	-	292.5	-	-
Starch 1500	-	-	292.5	-
Potato Starch	-	-	-	292.5
Mg Stearate	5.0	5.0	5.0	5.0
Cab-O-Sil	2.5	2.5	2.5	2.5
Total	500.0	500.0	500.0	500.0

The formulations were prepared by mixing Cab-O-Sil with the active ingredient in a suitable blender. Destructurized starch that had been screened through No. 30 screen m sh to remove aggregates, r a comparison starch, as appropriate, was then added and the components were then blended for 15 minutes in a high shear mixer. Finally, the lubricant was added, and the entire mixture was blended for 3 minutes without using an intensifier bar. The release profiles of the formulations are shown in Figure 19.

EXAMPLE 29

Formulations were prepared having the following compositions:

	(mg/tablet)	
Phenytoin Sodium	100.00	100.00
Dest. Starch	146.25	-
Potato Starch	-	146.25
Mg Stearate	2.50	2.50
Cab-O-Sil	1.25	1.25
Total	250.00	250.00

The formulations were prepared by mixing Cab-O-Sil with the active ingredient in a suitable blender. Destructurized starch that had been screened through No. 30 screen mesh to remove aggregates, or a comparison starch, as appropriate, was then added and the components were then blended for 15 minutes in a high shear mixer. Finally, the lubricant was added, and the entire mixture was blended for 3 minutes without using an intensifier bar, although 900 ml of distilled water was used to aid in mixing. The release profiles of the formulations are shown in Figure 20.

EXAMPLE 30

Formulations were prepared having the following compositions:

	(mg/tablet)			
Gemfibrozil	300	300	300	300
Dest. Starch	291	-	-	-
Merigel XX	-	291	-	-
Pregel. Starch	-	-	291	-
Potato Starch	-	-	-	291
Mg Stearate	6	6	6	6
Cab-O-Sil	3	3	3	3
Total	600	600	600	600

The formulations were prepared using the standard USP method using 2 paddles at 100 rpm at 37 degrees C. The formulations were tested both in environments containing pH buffer of 7.5 and in buffered solutions (pH 7.5) containing intestinal enzymes, including amylases. The release profiles of the formulations are shown in Figures 21 and 22.

EXAMPLE 31

Formulations were prepared having the following compositions:

	(mg/tablet)	
Gemfibrozil	300.0	300.0
Dest. Starch	291.0	143.25
Mg Stearate	6.0	4.50
Cab-O-Sil	3.0	2.25
Total	600.0	450.00

The formulations were prepared using the standard USP meth d using 2 paddles at 100 rpm at 37 degrees C. The formulations were tested both in environments containing pH buffer of 7.5 and in buffered soluti ns (pH 7.5) containing intestinal enzymes, including amylases. The release profiles of the formulations are shown in Figures 23 and 24.

EXAMPLE 32

Formulations were prepared having the following compositions:

	(mg/tablet)			
Gemfibrozil	300	300	300	300
Sodium Carbonate	-	12	30	150
Dest. Starch	291	279	261	141
Mg Stearate	6	6	6	6
Cab-O-Sil	3	3	3	3
Total	600	600	600	600

The formulations were prepared using the standard USP method using 2 paddles at 100 rpm at 37 degrees C. The formulations were tested in an environment containing pH buffer of 7.5. The release profiles of the formulations are shown in Figure 25.

EXAMPLE 33

Formulations were prepared having the following compositions:

(mg/tablet)

Gemfibrozil	300	300	300
Dest. Starch	291	141	141
Mg Carbonate	-	150	-
Na Carbonate	-	-	150
Mg Stearate	6	6	6
Cab-O-Sil	3	3	3
Total	600	600	600

The formulations were prepared using the standard USP method using 2 paddles at 100 rpm at 37 degrees C. The formulations were tested both in environments containing pH buffer of 7.5 and in buffered solutions (pH 7.5) containing intestinal enzymes, including amylases. The release profiles of the formulations are shown in Figures 26 and 27.

We claim:

1. A controlled release pharmaceutical composition comprising (i) a matrix comprising starch having been processed under shear at temperatures of about 80°C to about 240°C in a closed volume wherein the water content of said matrix was maintained at about 5% to about 45% by weight based on the starch/water mix and (ii) a pharmaceutically active ingredient, wherein said matrix is in intimate contact with said active ingredient and wherein said matrix and pharmaceutically active ingredient are present in amounts sufficient to control the release of the pharmaceutically active ingredient in an effective dose.

2. The composition of claim 1 wherein the temperatures of processing the starch range from about 130°C to about 160°C.

3. The composition of claim 1 wherein the starch is selected from the group consisting of native starch, chemically modified starch, genetically modified starch and mixtures thereof.

4. The composition of claim 3 wherein the starch is selected from the group consisting of potato starch, corn starch, rice starch, tapioca starch, rye starch, oat starch, wheat starch, waxy maize starch, and mixtures thereof.

5. The composition of claim 1 wherein the pharmaceutical active is present in a therapeutically effective amount.

6. The composition of claim 5 wherein the pharmaceutical active is water-soluble.

7. The composition of claim 5 wherein the pharmaceutical active is substantially water-insoluble.

8. The composition f claims 6 r 7 wherein the pharmaceutical active is selected from at least one of the following groups: ACE inhibitors; anti-anginal drugs; anti-arrhythmias; anti-asthmatic; anti-cholesterolemic; anti-convulsants; anti-depressants; anti-diarrhea preparations; anti-histamines; anti-hypertensive drugs; anti-infectives; anti-inflamatory agents; anti-lipid agents; anti-manics; anti-nauseants; anti-stroke agents; anti-thyroid preparations; anti-tumor drugs; anti-tussives; anti-uricemic drugs; anti-viral agents; acne drugs; alkaloids; amino acid preparations; anabolic drugs; analgesics; anesthetics; antacids; antiarthritics; antibiotics; anticoagulants; antiemetics; antiobesity drugs; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotic drugs; anxiolytic agents; appetite stimulants; appetite suppressants; beta blocking agents; bronchodialators; cardiovascular agents; cerebral dilators; chelating agents; cholycistekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; erythropoietic drugs; expectorants; fertility agents; fungicides; gastro-intestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypnotics; hypoglycemic agents; laxatives; migraine treatments; mineral supplements; mucolytics; narcotics; neuroleptics; neuromuscular drugs; NSAIDS; nutritional additives; peripheral vaso-dilators; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vaso-constrictors; vaso-dilators; vertigo agents; vitamins; and wound healing agents and mixtures thereof.

9. The composition of claim 6 wherein the water-soluble drug has a solubility of one part drug for up to 30 parts solvent.

10. The composition of claim 7 wherein the substantially water-insoluble drug has a solubility of one part drug for greater than 30 parts solvent.

11. The composition of claim 1 further comprising a material selected from the group consisting of excipients, extenders, lubricants, disintegrating agents, stabilizers, foaming agents, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, antiadherents, acidulents, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof.

12. The composition of claim 1 in an oral dosage form.

13. The composition of claim 12 in a compressed tablet form.

14. The composition of claim 12 forming a capsule.

15. The composition of claim 12 contained in a capsule.

16. The composition of claim 1 in a powder or granulated form.

17. The composition of claim 12 in a solid, semi-solid or gel form.

18. The composition of claim 12 in a syrup, suspension or liquid form.

19. The composition of claim 1 in an injectable form.

20. The composition of claim 1 in a dosage form useful for transdermal delivery.

21. The compositi n f claim 1 in an implantable dosage form.

22. The composition of claim 1 in an aerosol form.

23. The composition of claim 17 in a suppository dosage form.

24. A method of delivering a pharmaceutical agent to a plant, animal or insect at a controlled rate comprising administering to said plant, animal or insect a therapeutically effective amount of a composition comprising (i) a matrix comprising starch having been processed under shear at temperatures of about 110° to about 240°C in a closed volume wherein the water content of said matrix during processing was maintained at about 5% to about 45% by weight and (ii) a pharmaceutical active, wherein said matrix is in intimate contact with said active.

25. A method of preparing a controlled release pharmaceutical composition comprising forming an admixture of (i) starch which has been processed under shear at temperatures of about 110°C to about 240°C in a closed volume while the water content of said matrix was maintained at about 5% to about 45% by weight based on the starch/water mix; and (ii) a pharmaceutical active.

26. A method of preparing a controlled release therapeutic composition comprising mixing a therapeutic active with starch under sufficient conditions of shear, temperature, pressure and starch water content to substantially destroy the granular structure of said starch.

27. A controlled release therapeutic composition comprising (i) a matrix of starch which is substantially free of intact starch granules; and (ii) a therapeutic agent present in a therapeutically effective amount.

28. The therapeutic composition of claim 27 wherein the therap utic agent is selected from the group consisting of water-soluble and water-ins luble drugs.

29. The therapeutic composition of claim 27 wherein the starch is selected from the group consisting of native starches, chemically modified starches, genetically modified starches and mixtures thereof.

30. A controlled release composition useful for delivering therapeutic agents comprising (i) destructurized starch and (ii) a therapeutic agent, said destructurized starch being in intimate contact with the therapeutic agent.

31. The composition of claim 30 wherein the destructurized starch forms a matrix for said therapeutic agent.

32. The composition of claim 30 wherein the destructurized starch at least partially coats or enrobes the therapeutic agent.

33. The composition of claim 30 wherein the destructurized starch and the therapeutic agent form as aggregate or granulate.

34. The composition of claims 1, 24, 25 and 26 wherein a polyol is substituted for a portion of the water content of the starch.

35. The composition of claim 34 wherein the polyol is selected from the group consisting of glycerol, sorbitol and mixtures thereof.

36. A controlled release composition useful for controlling the release of pharmaceuticals, flavors, sweeteners, pesticides, poisons, agricultural products, growth hormones and sex hormones, comprising (i) a starch

melt; and (ii) a releasable ingredient selected from the group consisting of pharmaceuticals, flavors, sweeteners, pesticides, poisons, agricultural products, sex hormones, growth r gulators and mixtures thereof.

37. A controlled release comestible composition comprising: (i) a carrier base material comprising a solidified starch melt; and (ii) a releasable material selected from the group consisting of sweetening agents, flavor agents, food acids, fragrances, coloring agents, and mixtures thereof.

38. The controlled release composition of claim 37 incorporated into a chewing gum composition.

39. The controlled release composition of claim 37 incorporated into a confectionery or snack food composition.

40. The composition of claim 37 in the form of a foamed product.

41. A process of preparing a controlled release matrix useful for medicinal products, food products and agricultural products comprising (i) processing starch to obtain a melt, (ii) allowing the melt to solidify, (iii) cryogenically milling the solidified melt, and (iv) controlling the moisture content of the milled solidified melt to the desired level.

Figure 1.
Effect of Matrix Processing on the Dissolution of Tacrine HCl (12.8 mg) Tablets.
(0.1 N HCl; USP 2, 50 rpm; 37 c.)

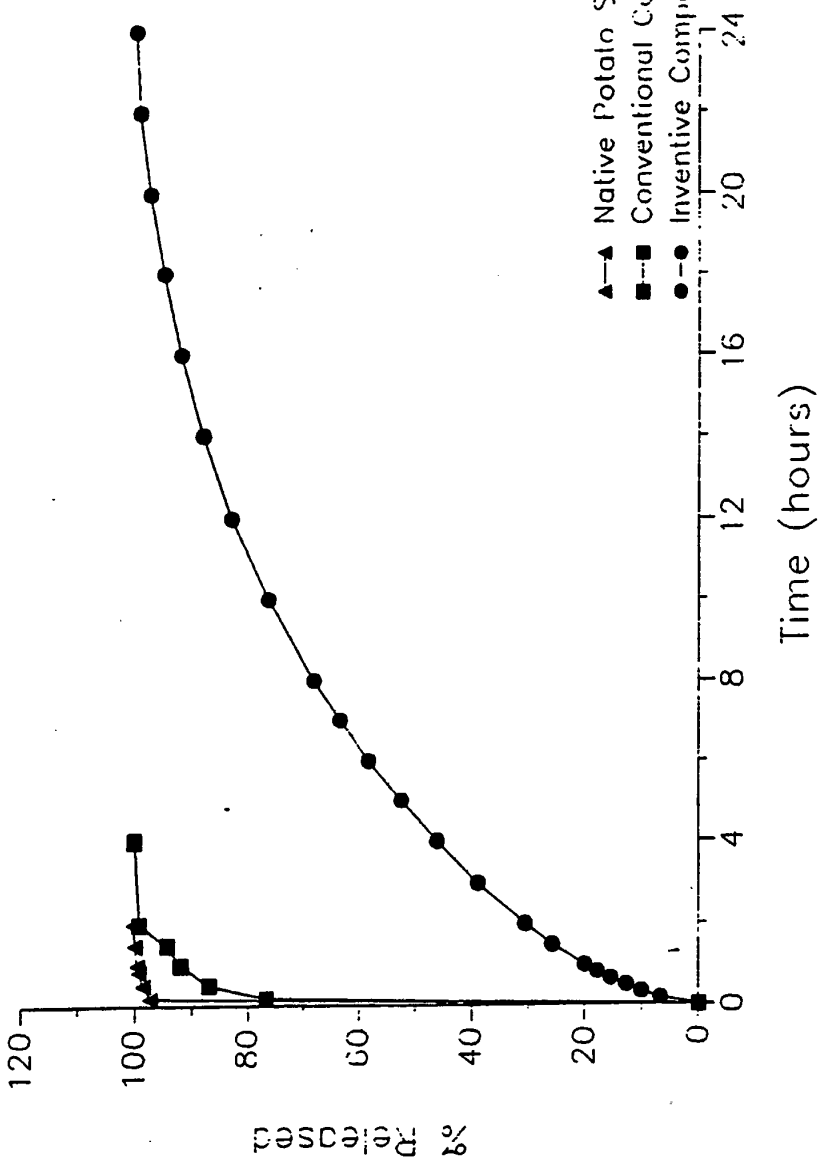


Figure 2.
Effect of Medium on Dissolution of Tacrine HCl (12.8 mg) Tablets Containing the Inventive Matrix (Example 1).
(USP 2, 50 rpm, 37 c)

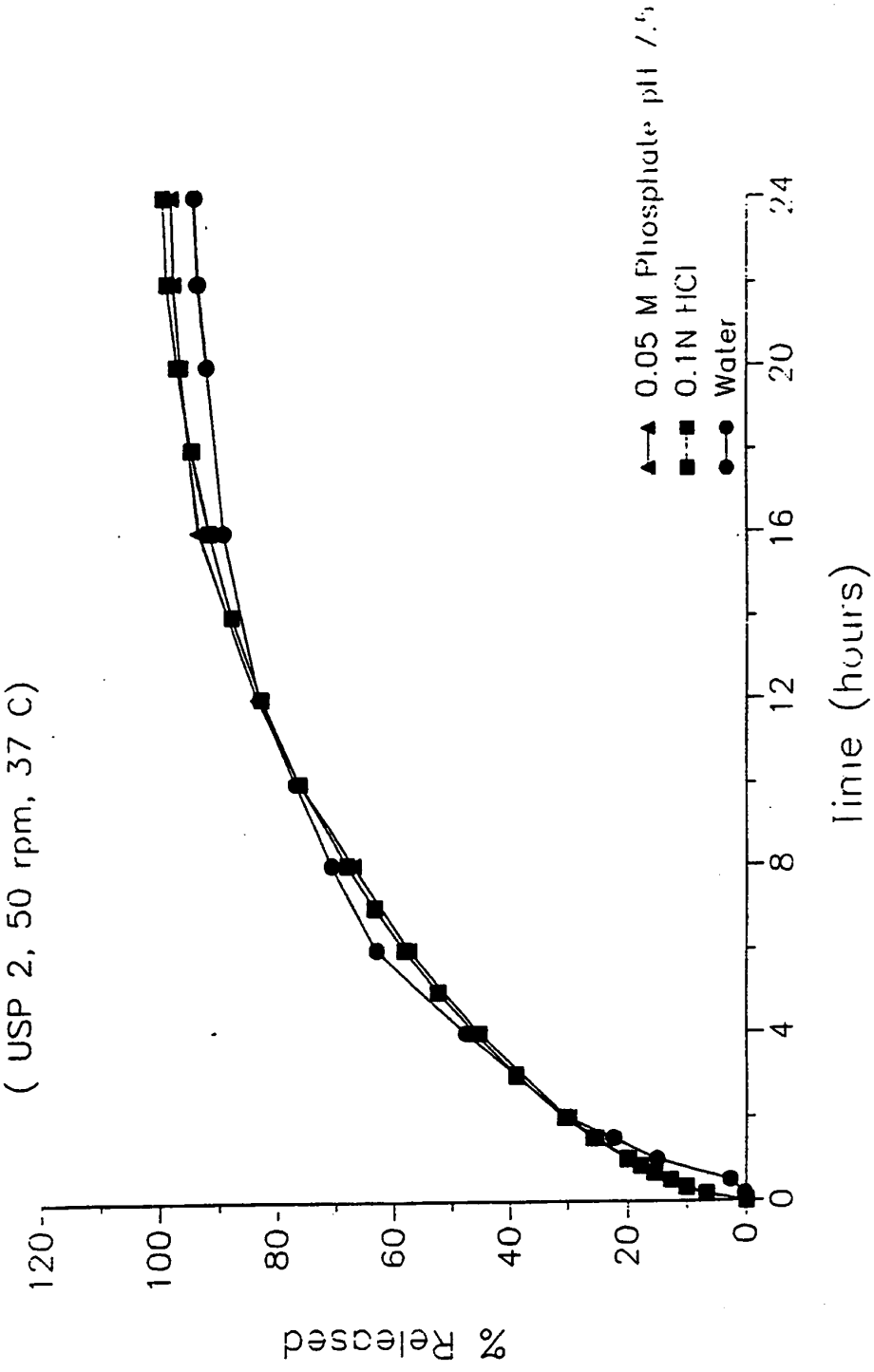


Figure 3.
Effect of the Apparatus on the Dissolution of Tacrine HCl (12.8 mg) Tablets containing the Inventive Matrix. (Example 1)
(0.1 N HCl; 37 C)

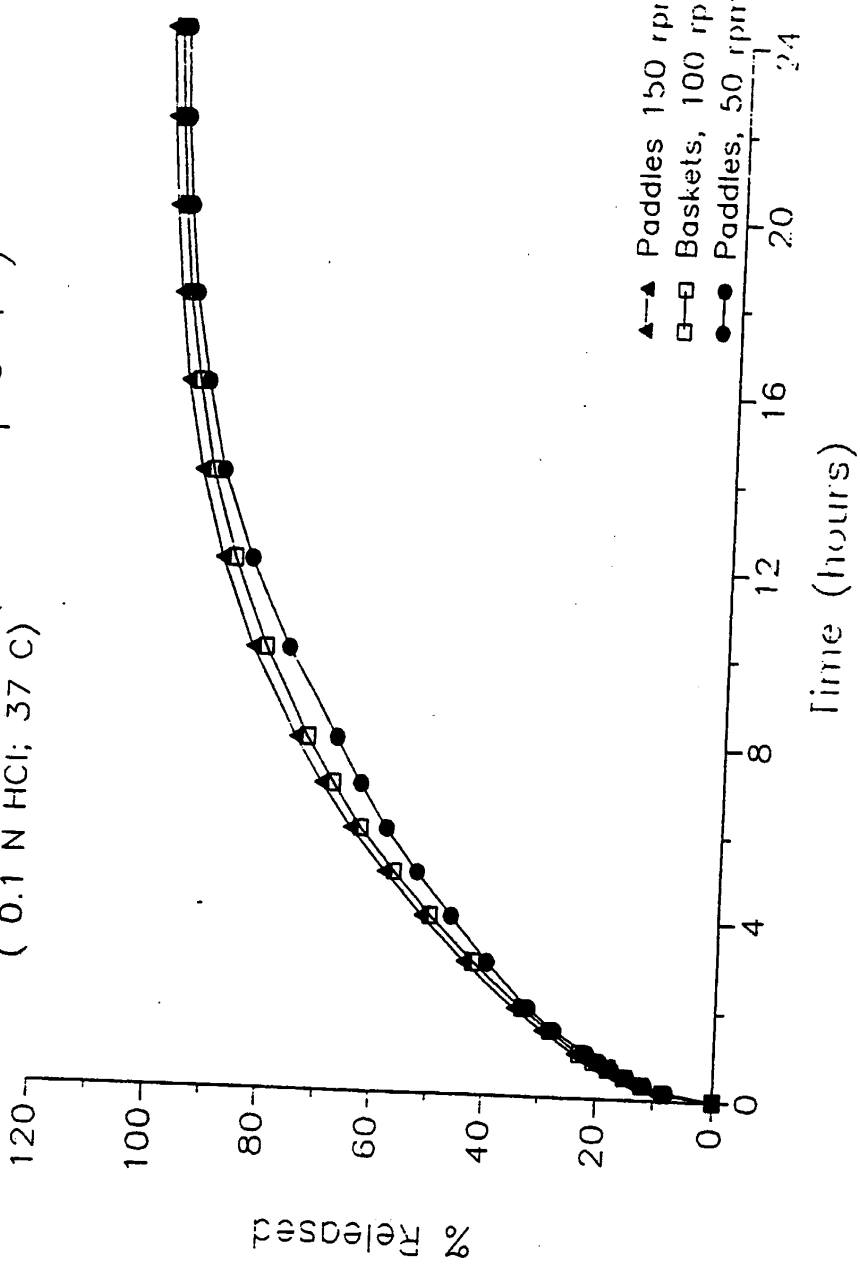


Figure 4.
Effect of Lubricant on Dissolution of Tacrine HCl (12.8 mg) Tablets Containing the Inventive Matrix.
(0.1 N HCl; USP 2, 50 rpm; 37 C.)

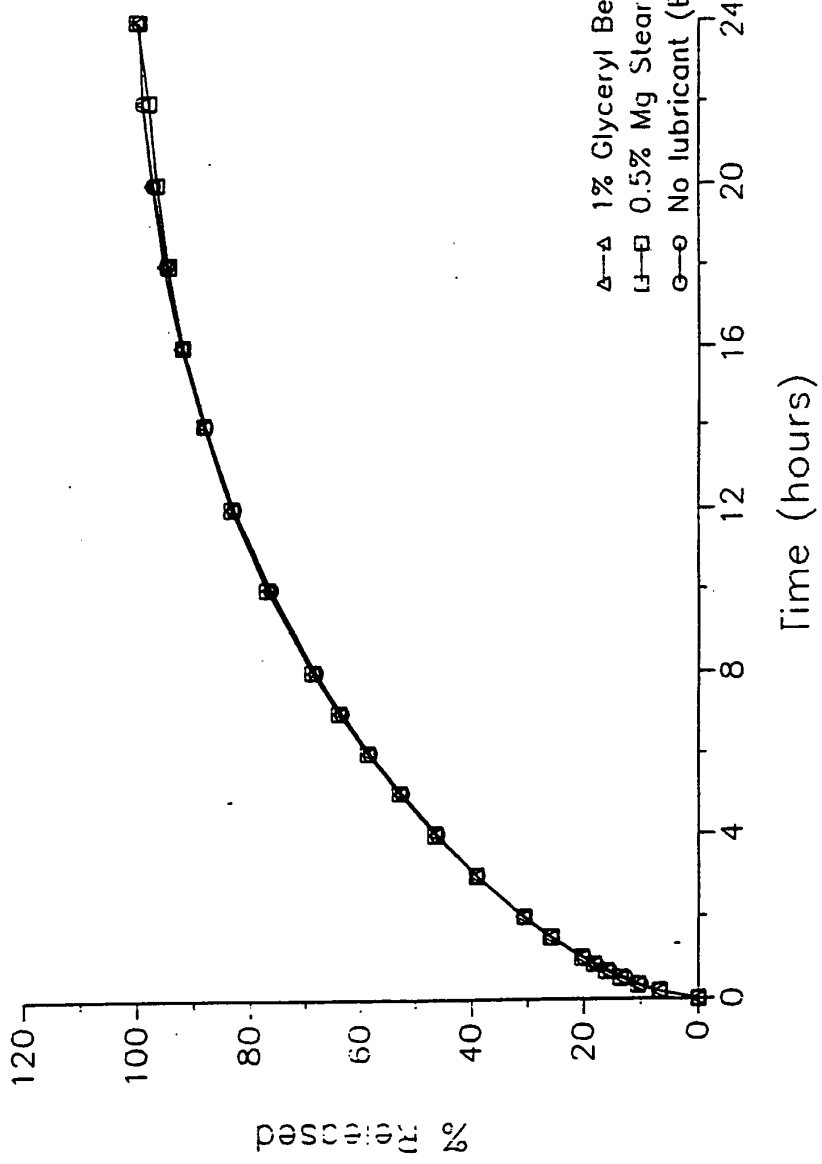


Figure 5.
Effect of Drug Loading on Dissolution of Tacrine HCl (51.2 mg) Tablets Containing the Inventive Matrix (Example 6).
(0.1 N HCl; USP 2, 50 rpm, 37 C)

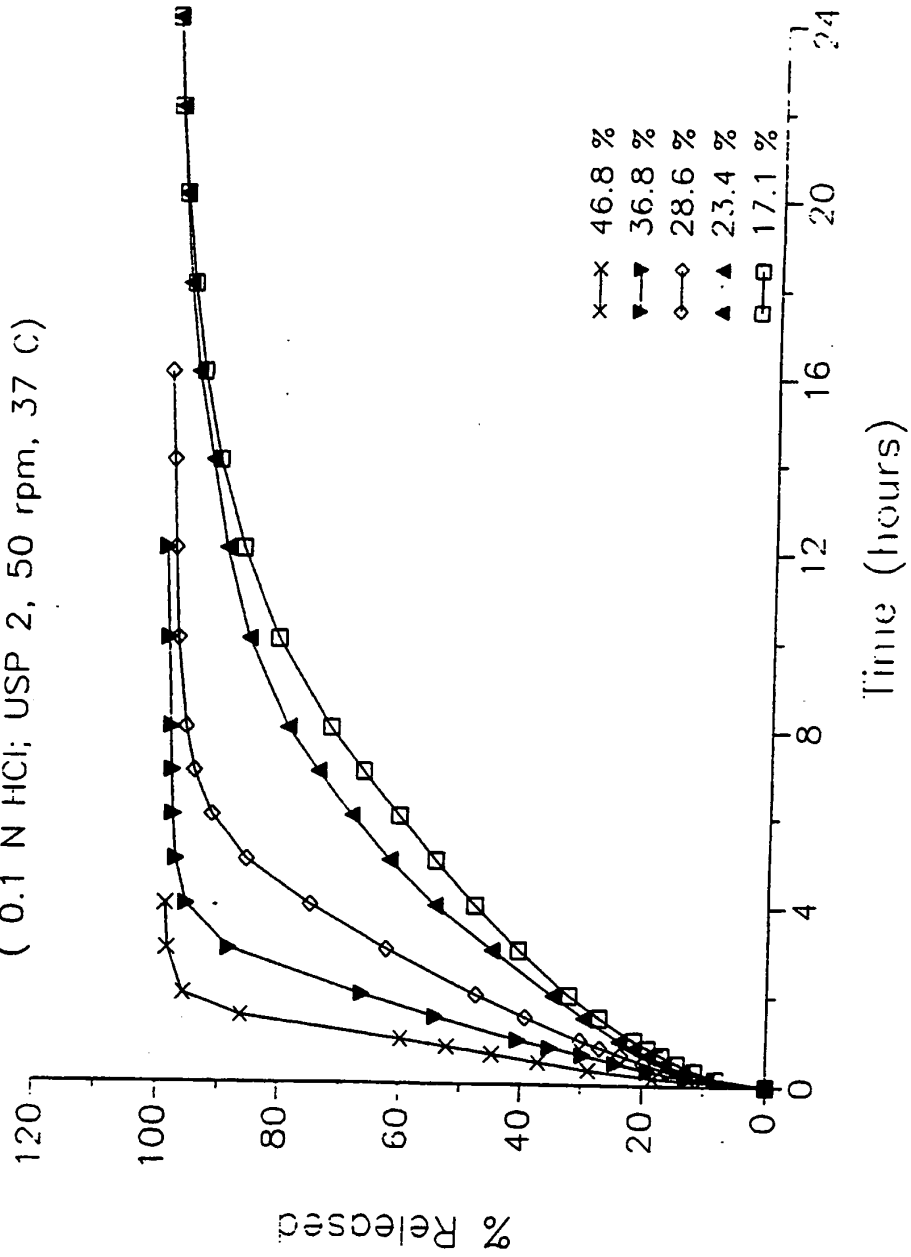


Figure 6.
Effect of Moisture Content on Dissolution of Tacrine HCl (12.8 mg) Tablets Containing the Inventive Matrix (Example 1).
(0.1 N HCl; USP 2, 50 rpm; 37 c)

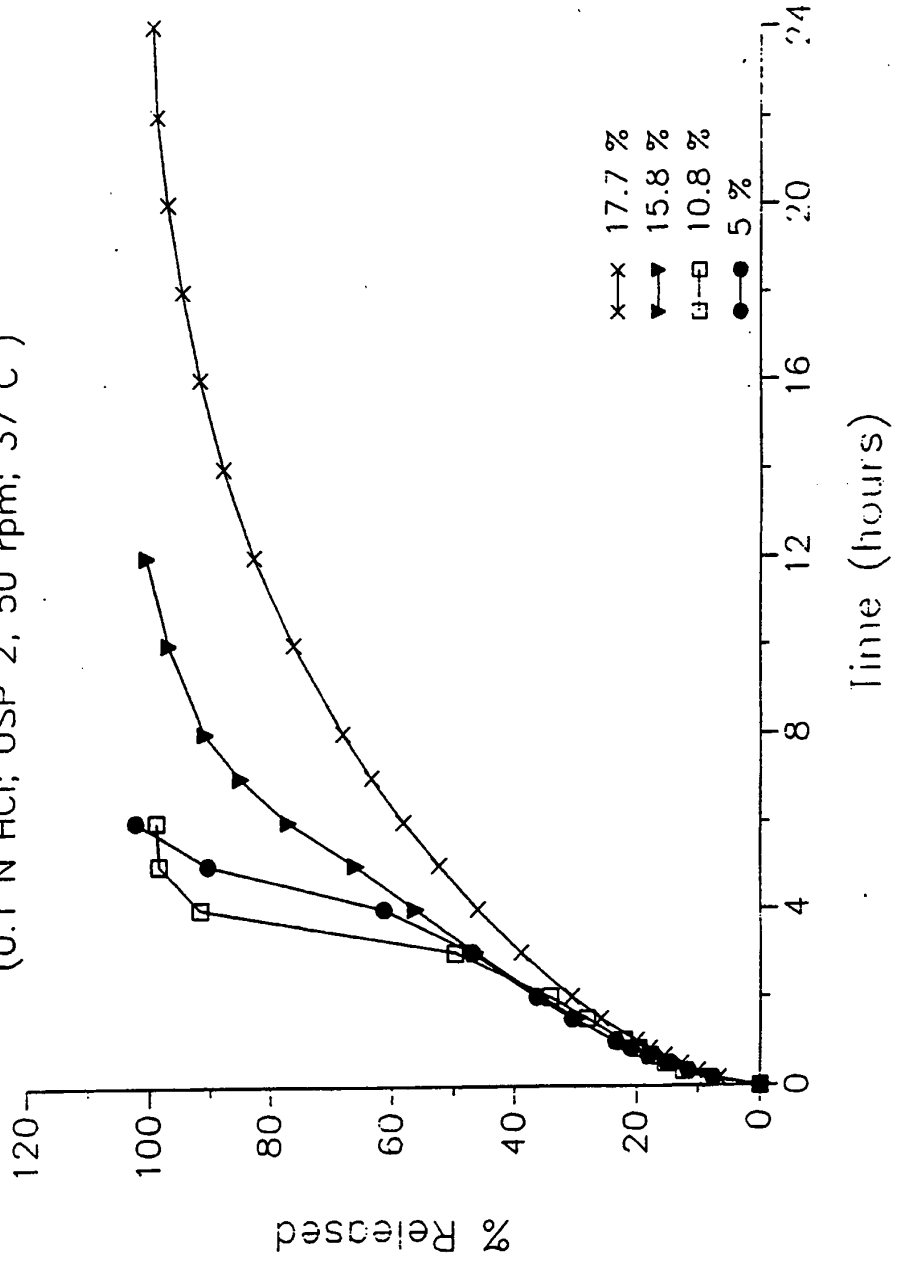


Figure 7.
Gemfibrozil Dissolution from Capsules Containing Inventive Composition or Conventional Corn Starch.
(0.05 M Phosphate Buffer pH 7.5; USP 2, 50 rpm)

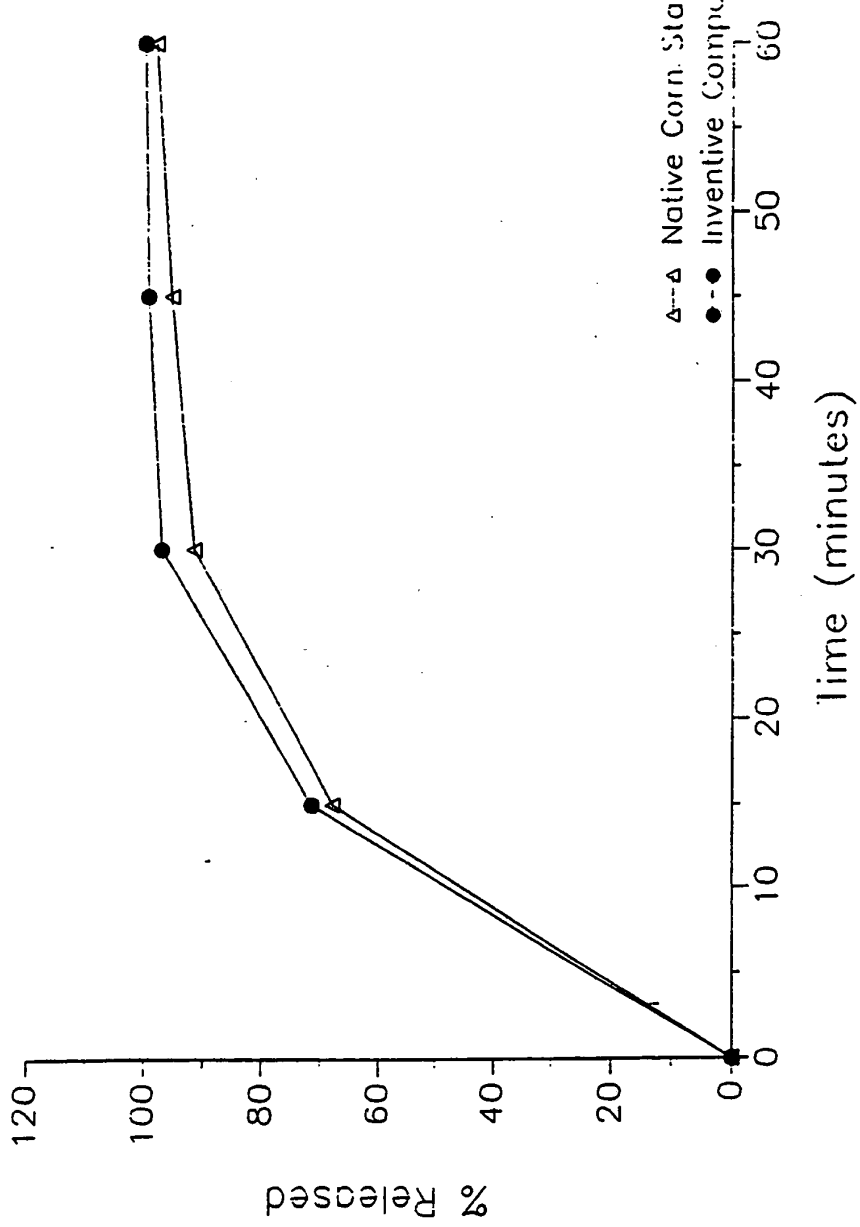


Figure 8.
Tacrine Dissolution from Capsules Containing Inventive Composition or Conventional Corn Starch.
(0.1 N HCl; USP 2, 50 rpm; 37 C)

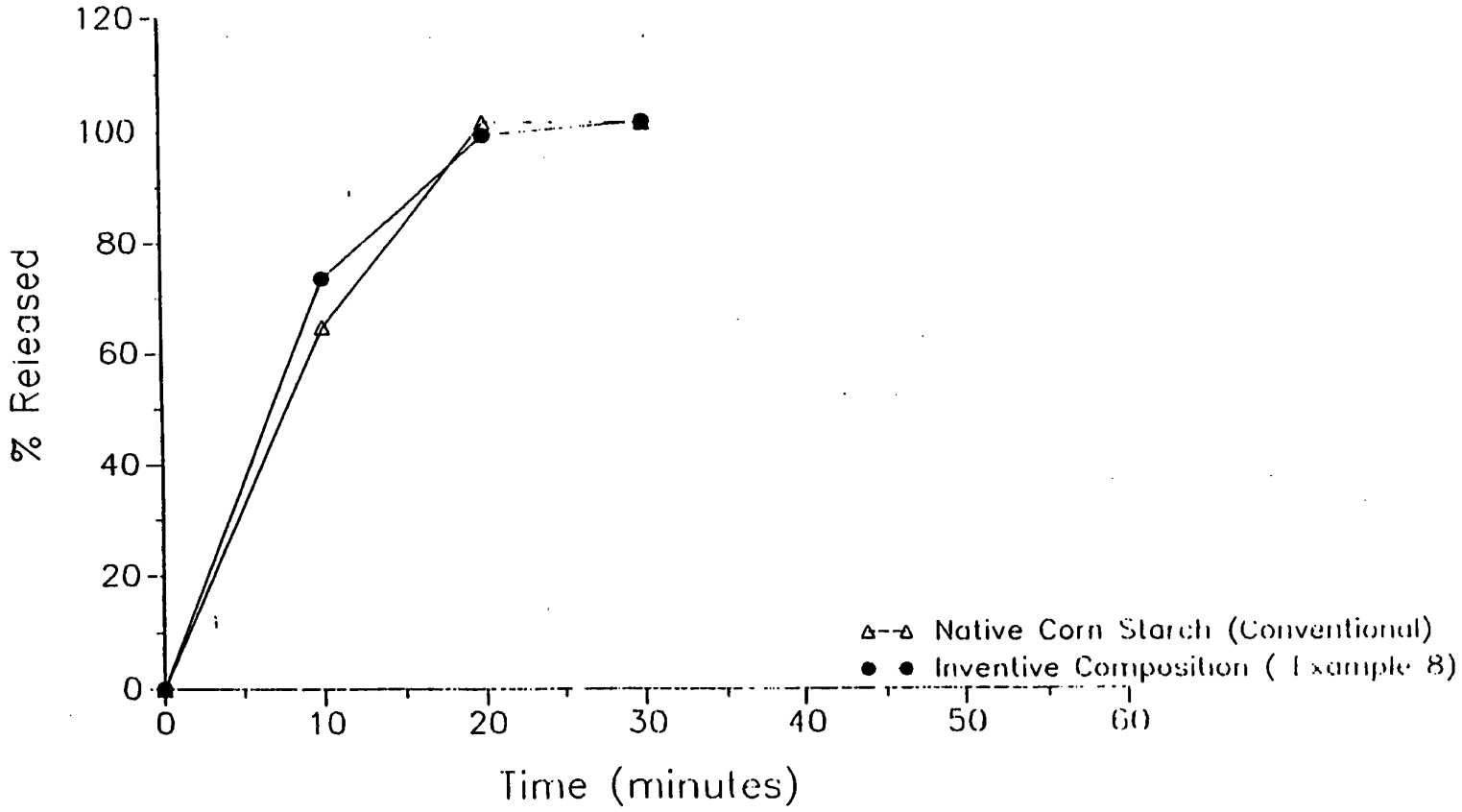


Figure 9.
Dissolution of Hydrochlorothiazide (25 mg) Tablets Containing the Inventive Matrix Using Two Different Apparata (Example 9) .
(0.1 N HCl; 37 C)

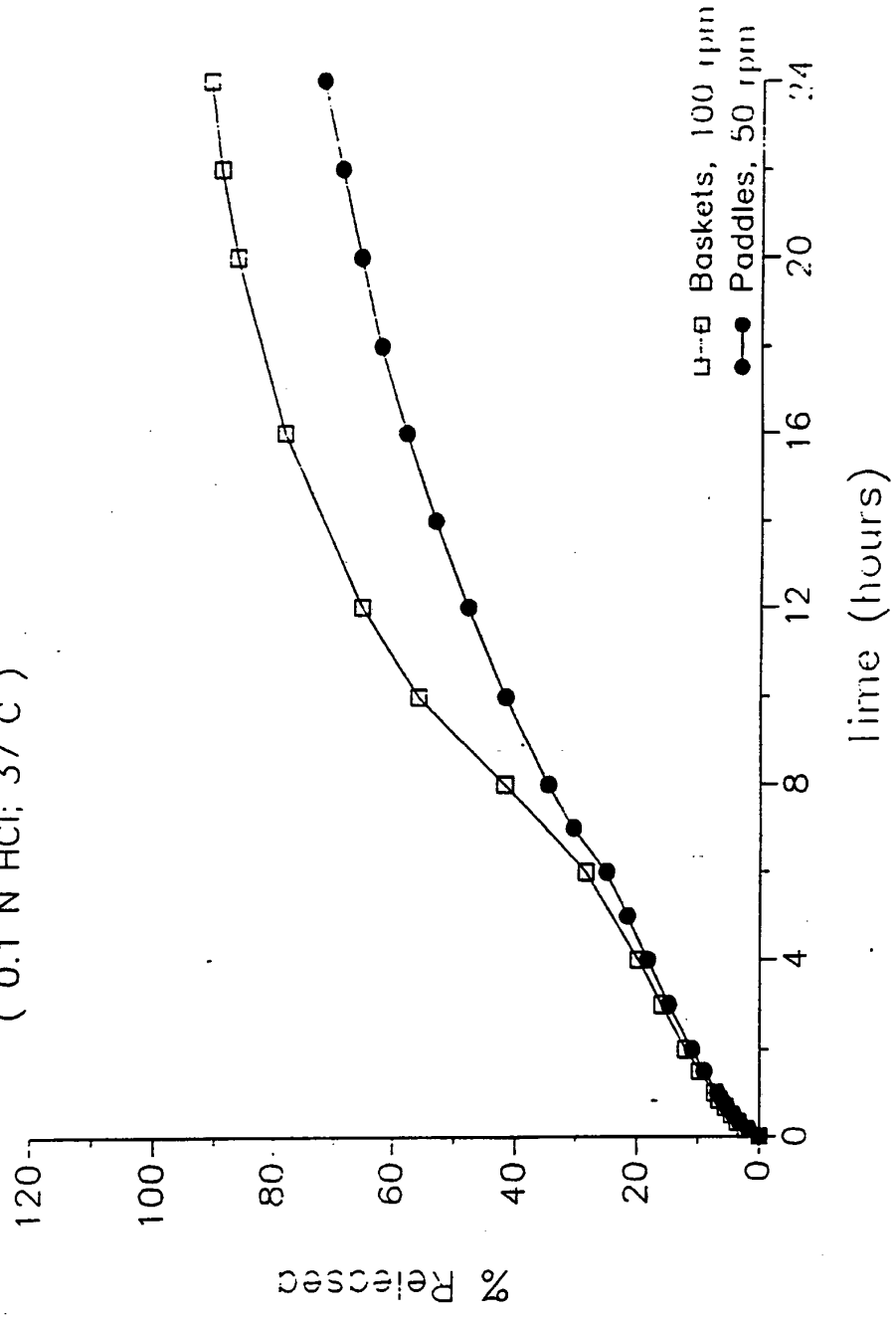


Figure 10.
Effect of Starch Processing Temperature on the Release Characteristics of Tacrine HCl (12.8 mg) Tablets (Example 10).
(0.1 N HCl; USP 2, 50 rpm, 37 C)

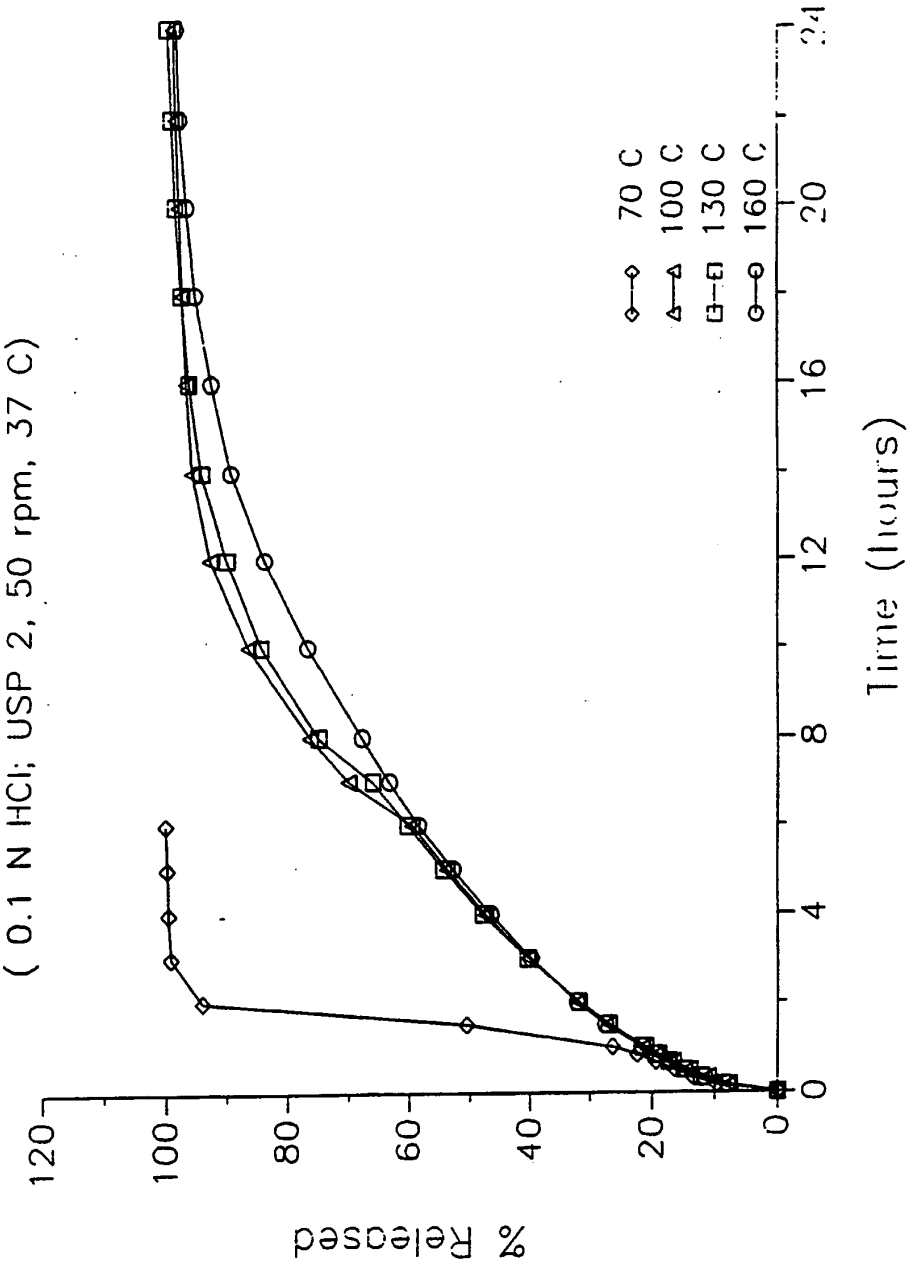


Figure 11.
Effect of Enzyme in the Medium on the Dissolution of Tacrine HCl (12.8 mg) Tablets Containing the Inventive Matrix (Example 11).
(USP 2, 50 rpm, 37 c)

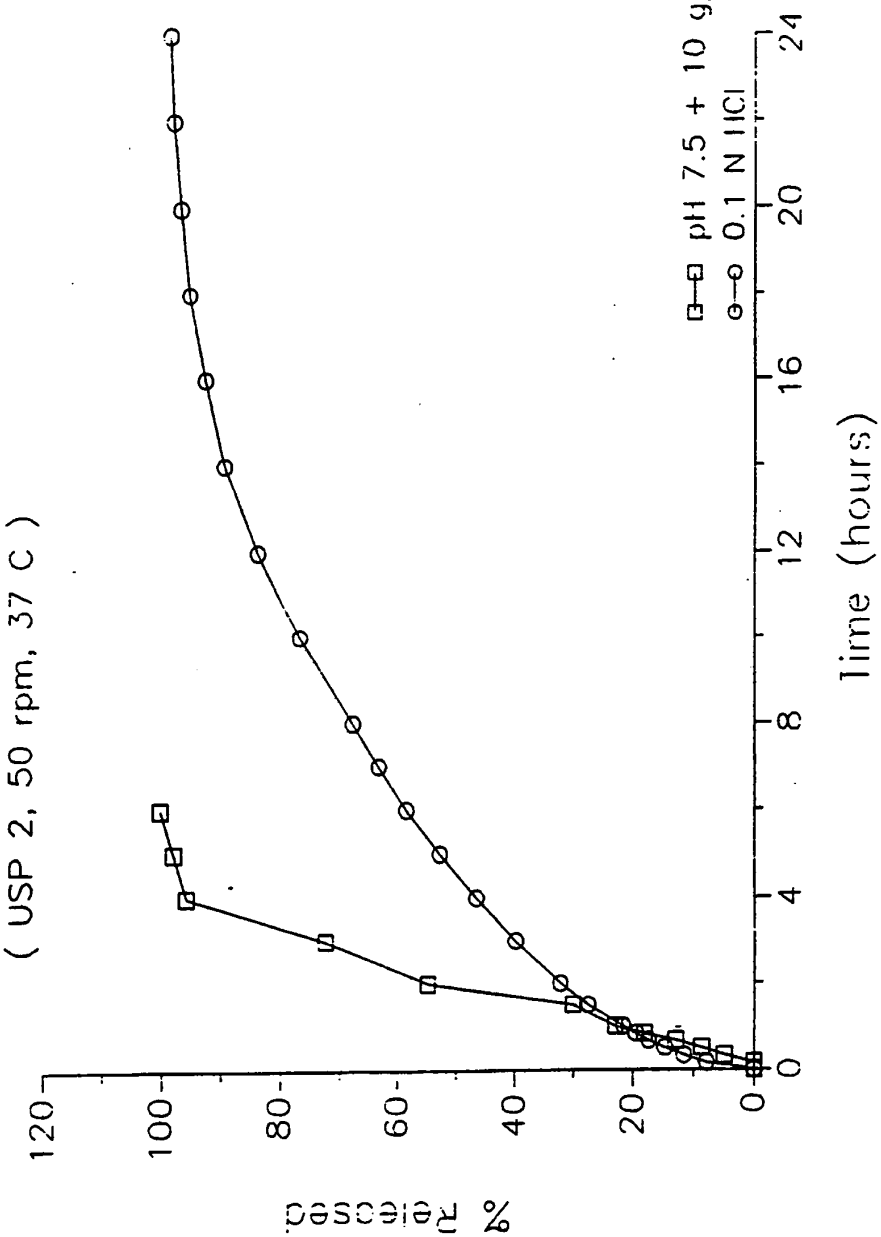


Figure 12.
Comparison of Inventive Matrix vs.Pregelatinized Starch on Tacrine HCl (12.8 mg) Tablets Dissolution (Example 18).

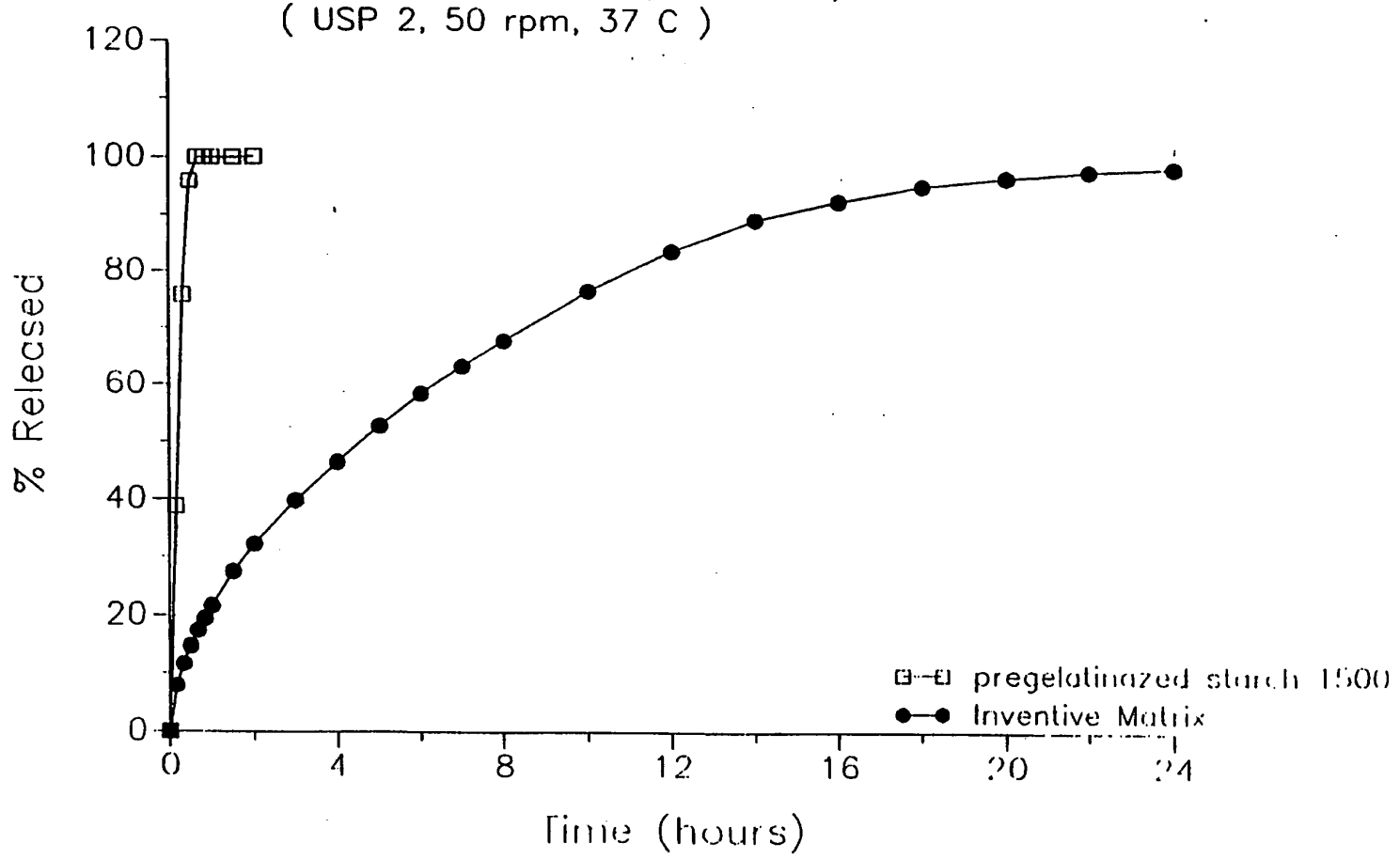


Figure 13.
Comparison of Inventive Matrix vs.Pregelatinized Starch on Theophylline Tablets Dissolution.
Tablet Lubricant: Na Benzoate (Example 19).
(USP 2, 50 rpm, 37 C)

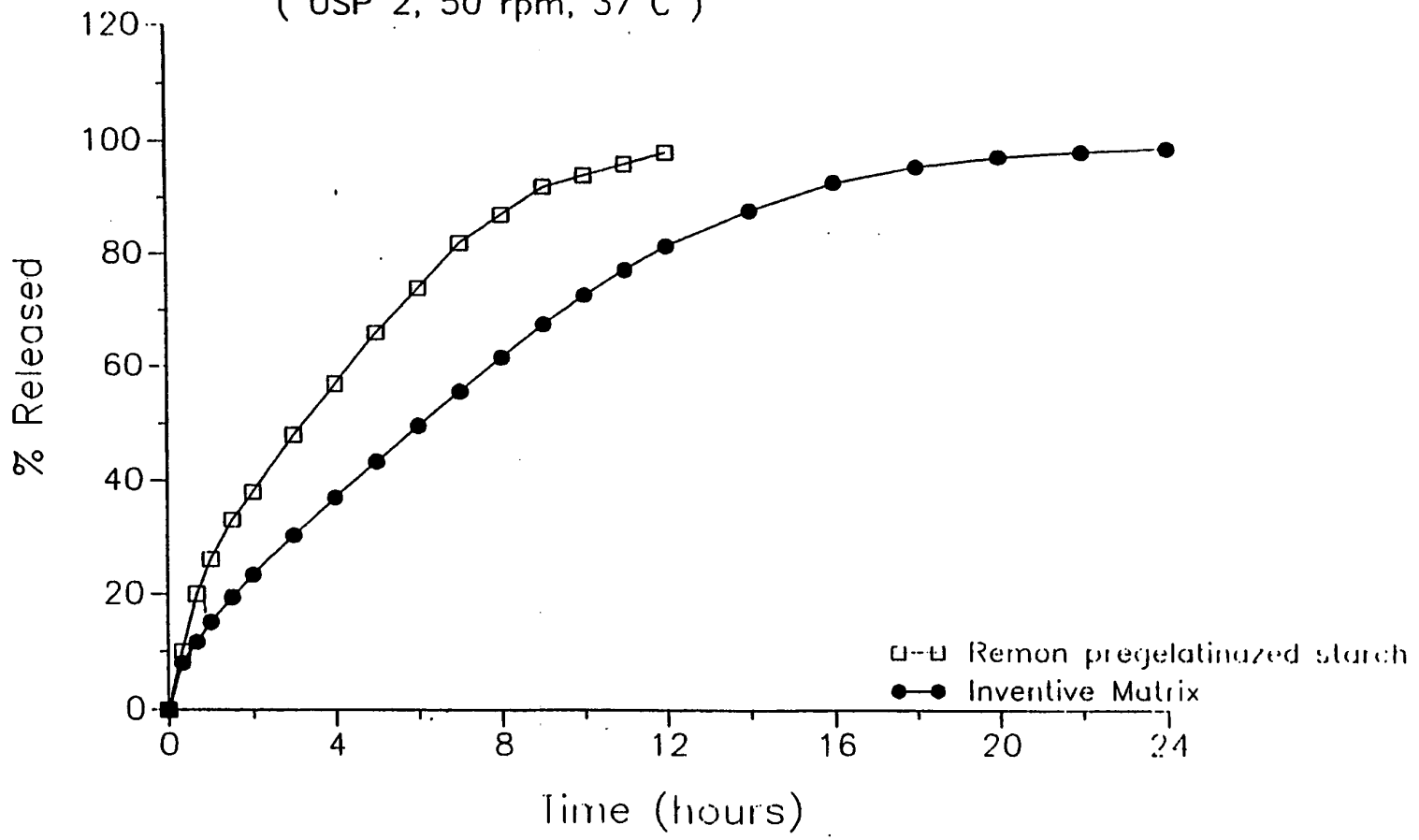


Figure 14.
Comparison of Inventive Matrix vs. Pregelatinized Starch on Theophylline Tablets Dissolution.
Tablet Lubricant: Mg Stearate (Example 20).
(USP 2, 50 rpm, 37 C)

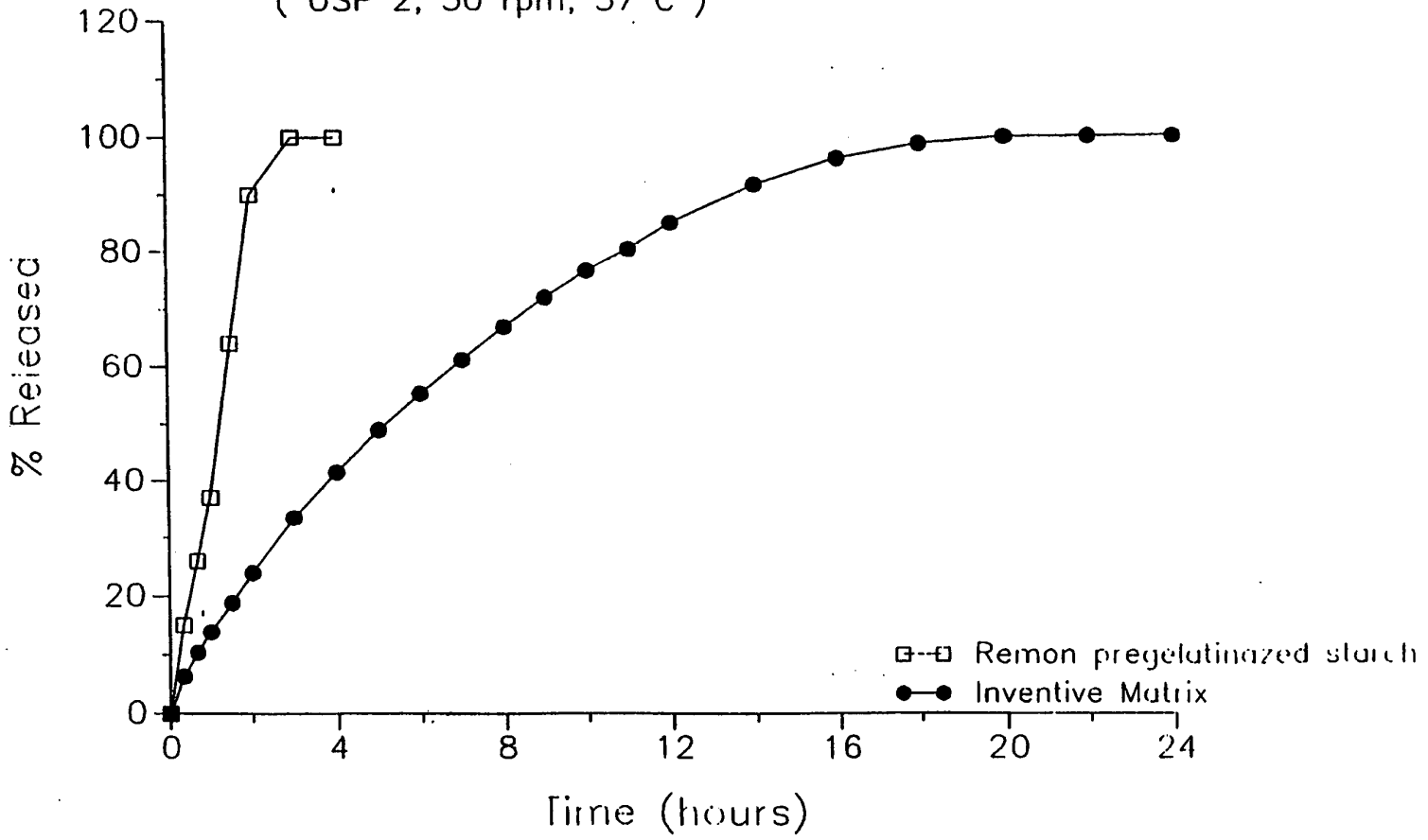


Figure 15.
Comparison of Inventive Matrix vs. Pregelatinized Starch on Theophylline Tablets Dissolution.
Tablet Lubricant: None (Example 21).
(USP 2, 50 rpm, 37 C)

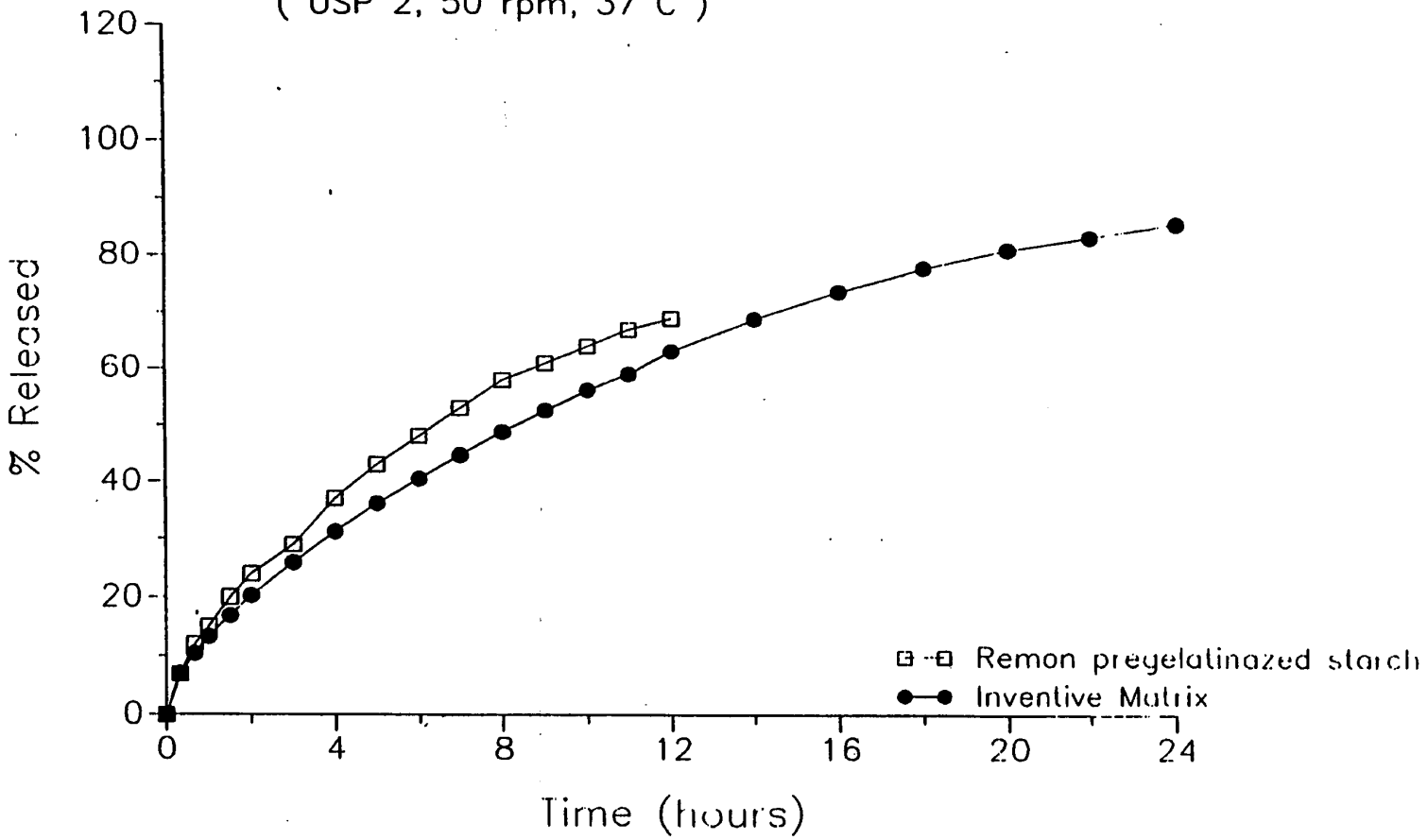


FIGURE 16

The Physical Approach: Oral and Parenteral

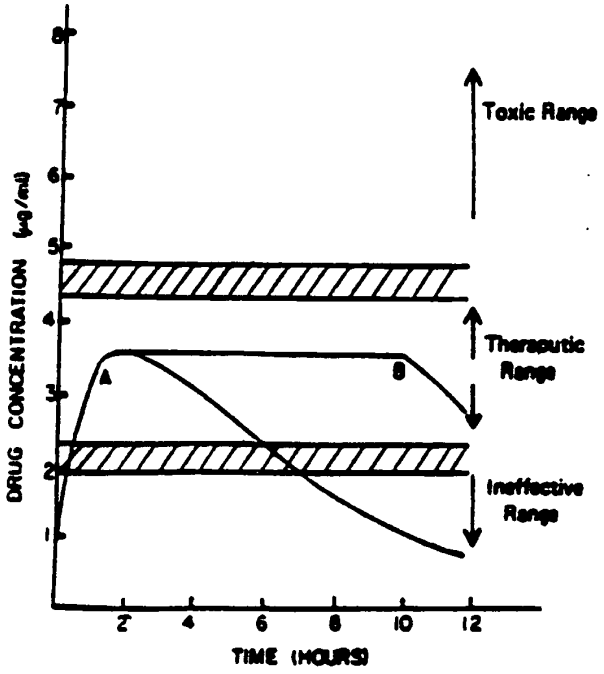


FIGURE 17

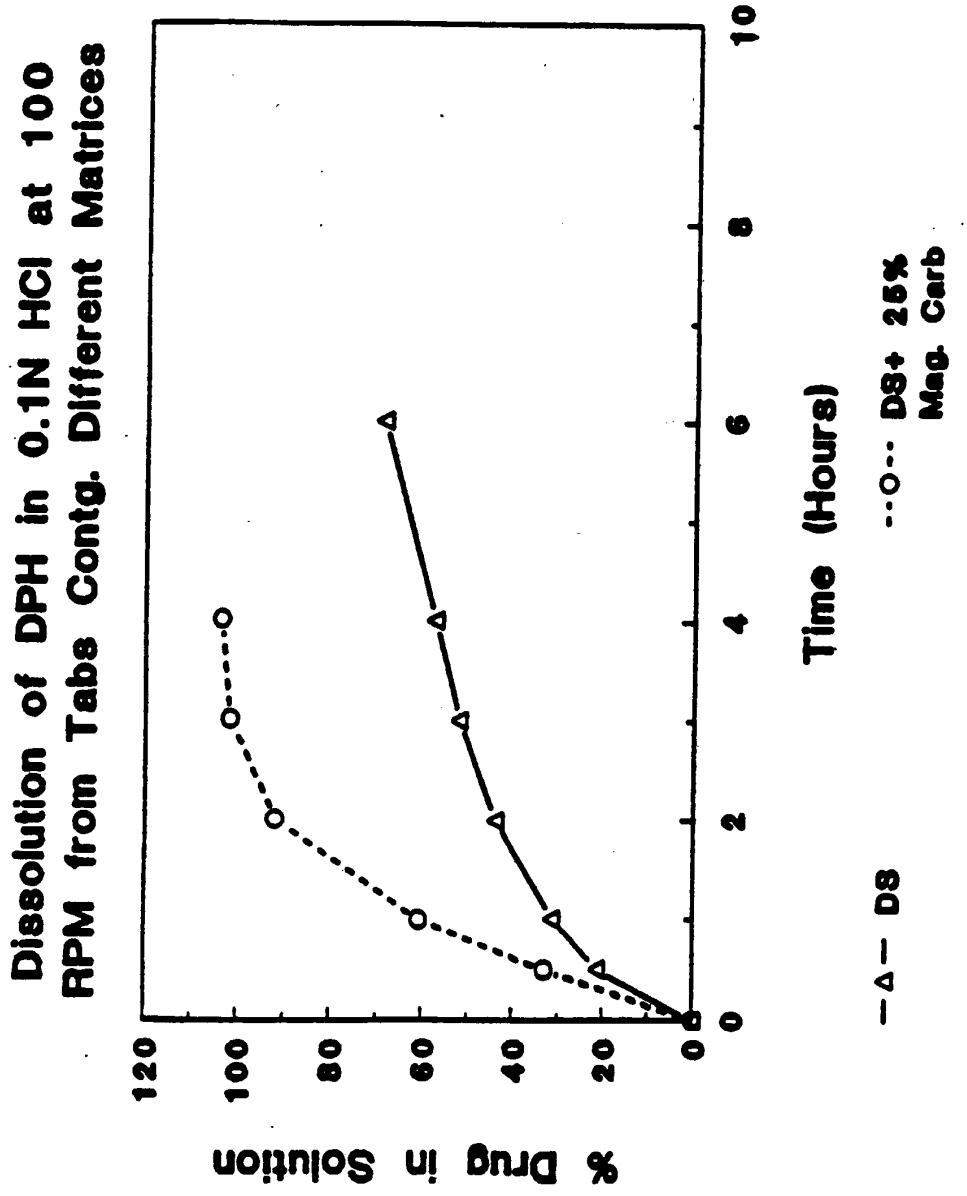

Dissolution of DPH in 0.1N HCl at 100 RPM from Tabs Contg. Different Matrices
% Drug in Solution
120
100
80
60
40
20
0
0
2
4
6
8
10
Time (Hours)
—△— DS
--○-- DS+ 25% Mag. Carb

FIGURE 18

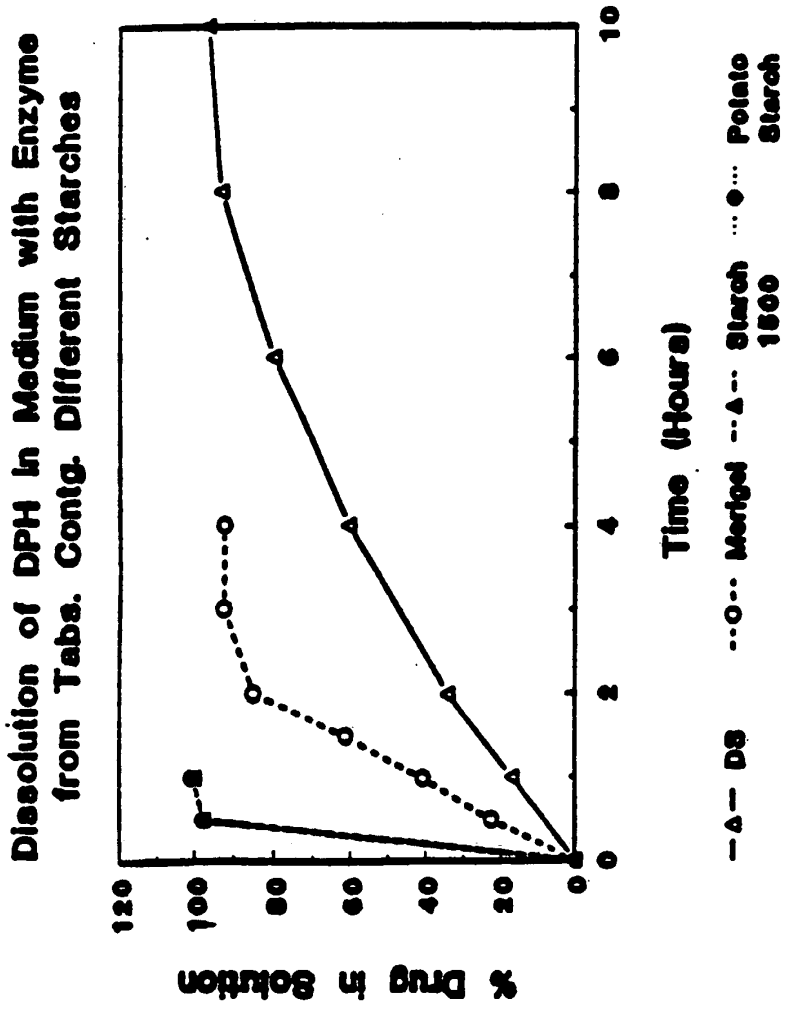

Dissolution of DPH in Medium with Enzyme from Tabs. Contg. Different Starches
% Drug in Solution
120
100
80
60
40
20
0
0
2
4
6
8
10
Time (Hours)
—▲— DS
--O-- Merigel
--▲-- Starch 1500
--●-- Potato Starch

FIGURE 19

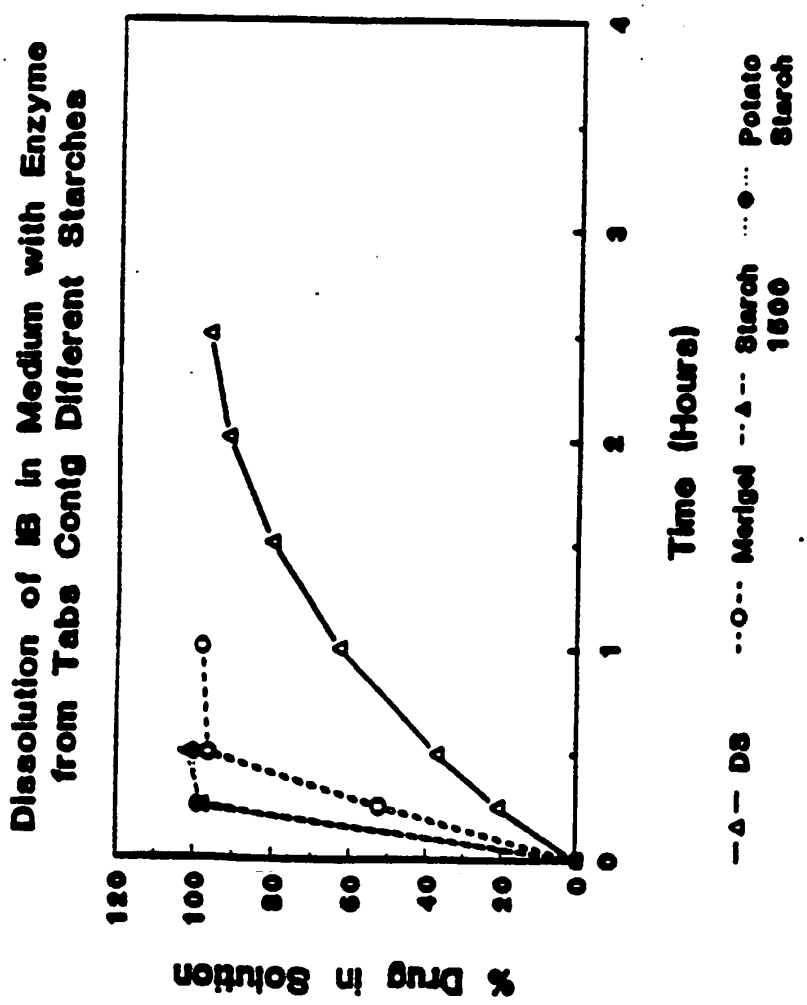

Dissolution of IB in Medium with Enzyme
from Tabs Contg Different Starches
% Drug in Solution
120
100
80
60
40
20
0
0
1
2
3
4
Time (Hours)
—△— DS
--○-- Merigel
--△-- Starch 1500
---●--- Potato Starch

FIGURE 20

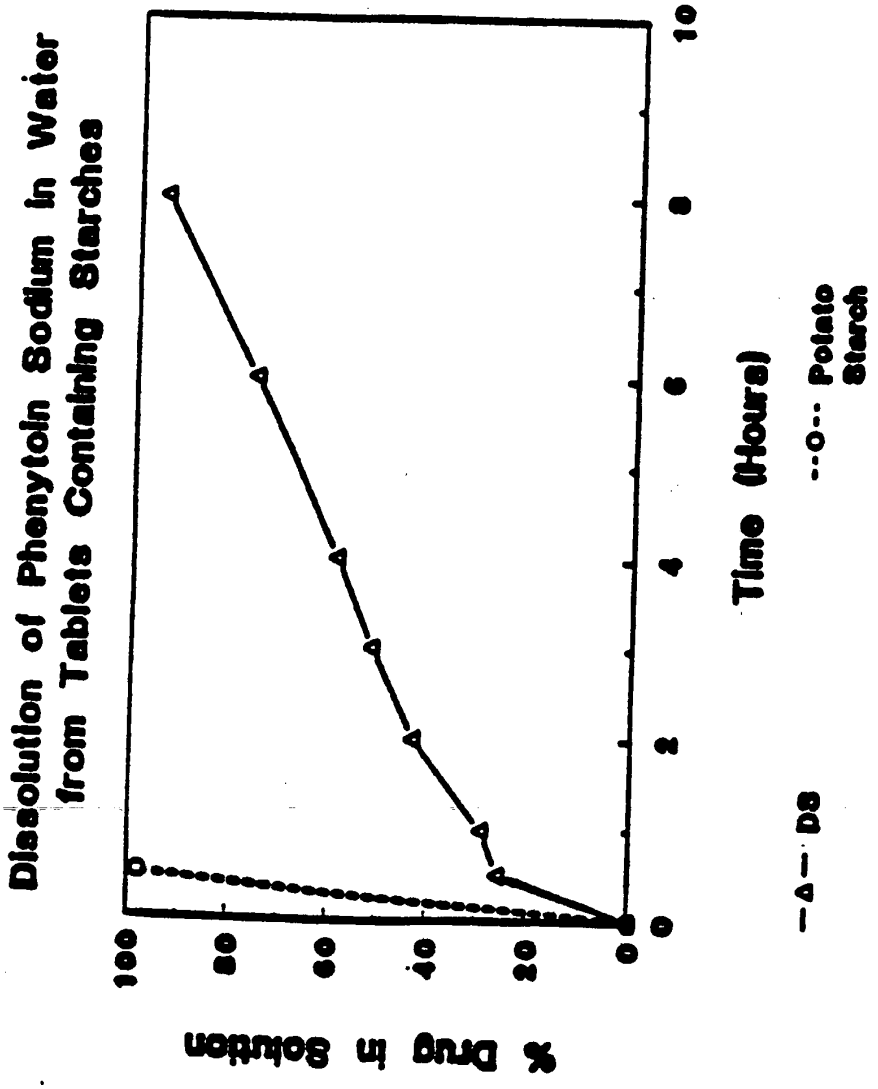

Dissolution of Phenytoin Sodium in Water
from Tablets Containing Starches
% Drug in Solution
100
80
60
40
20
0
0
2
4
6
8
10
Time (Hours)
—Δ— DS
--O-- Potato
Starch

FIGURE 21

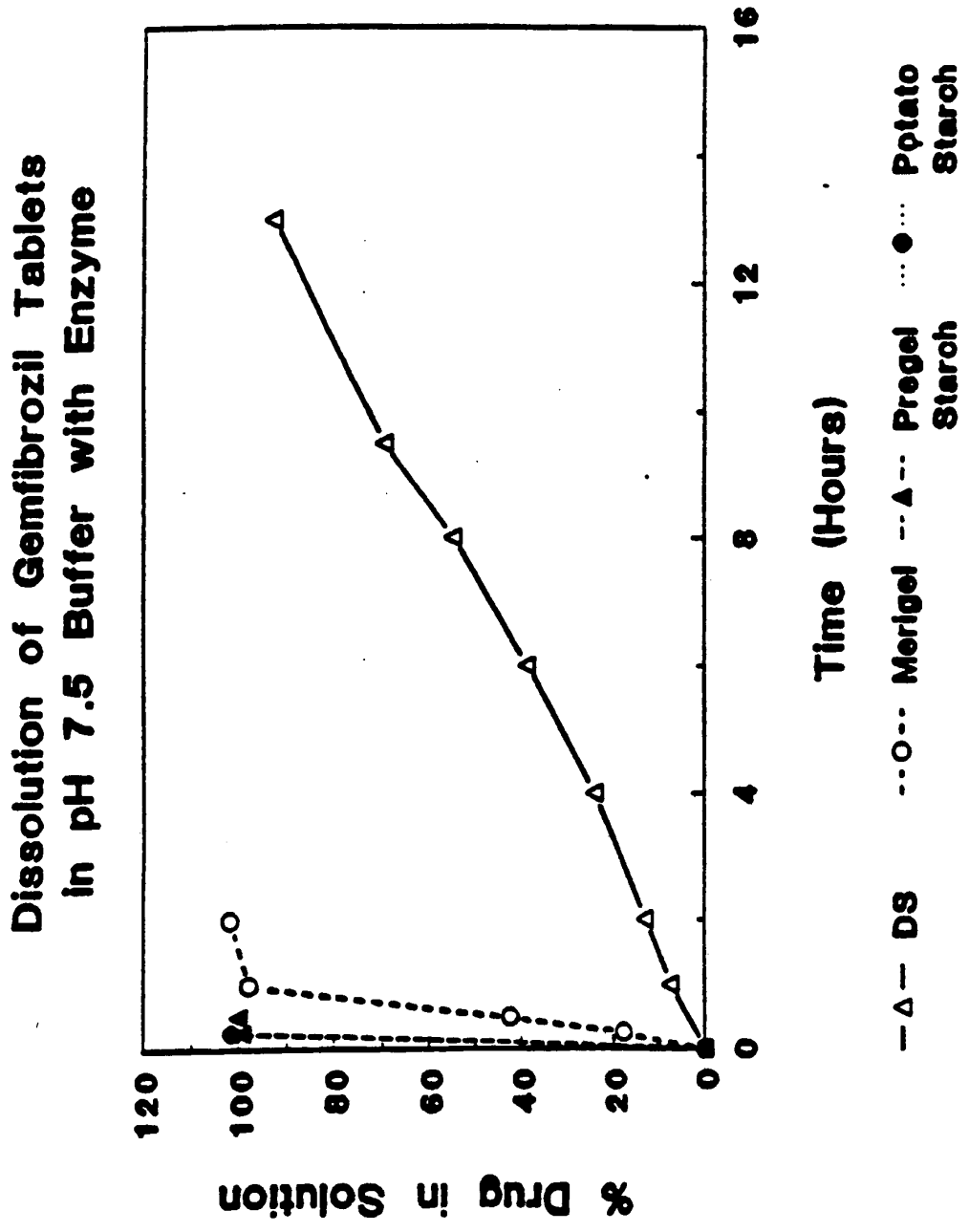
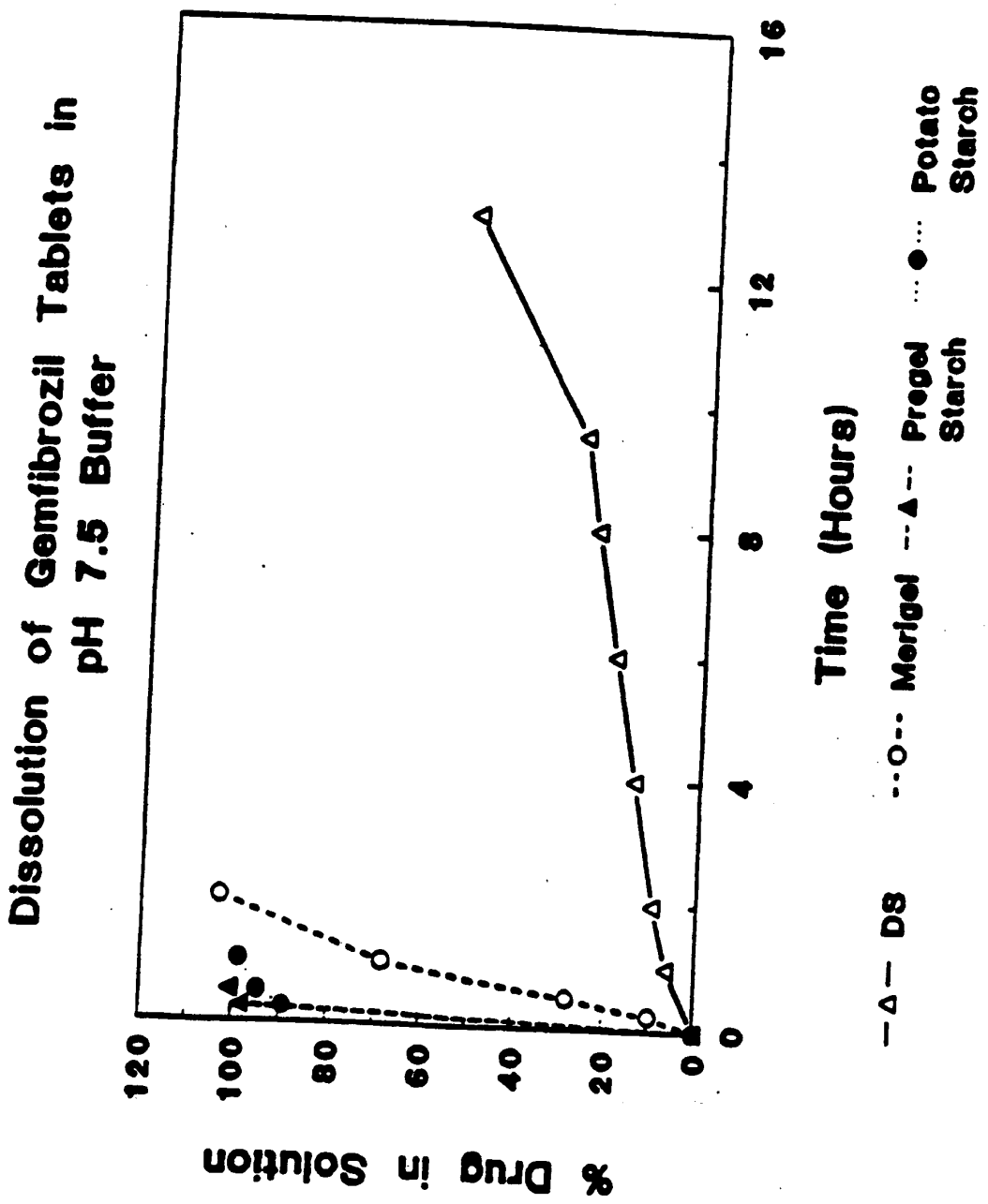

Dissolution of Gemfibrozil Tablets
in pH 7.5 Buffer with Enzyme
% Drug in Solution
120
100
80
60
40
20
0
0
4
8
12
16
Time (Hours)
—△— DS
--○-- Merigel
--▲-- Pregel Starch
···●··· Potato Starch

FIGURE 22


Dissolution of Gemfibrozil Tablets in pH 7.5 Buffer
% Drug in Solution
120
100
80
60
40
20
0
0
4
8
12
16
Time (Hours)
—△— DS
--○-- Merigel
--▲-- Pregel Starch
···●··· Potato Starch

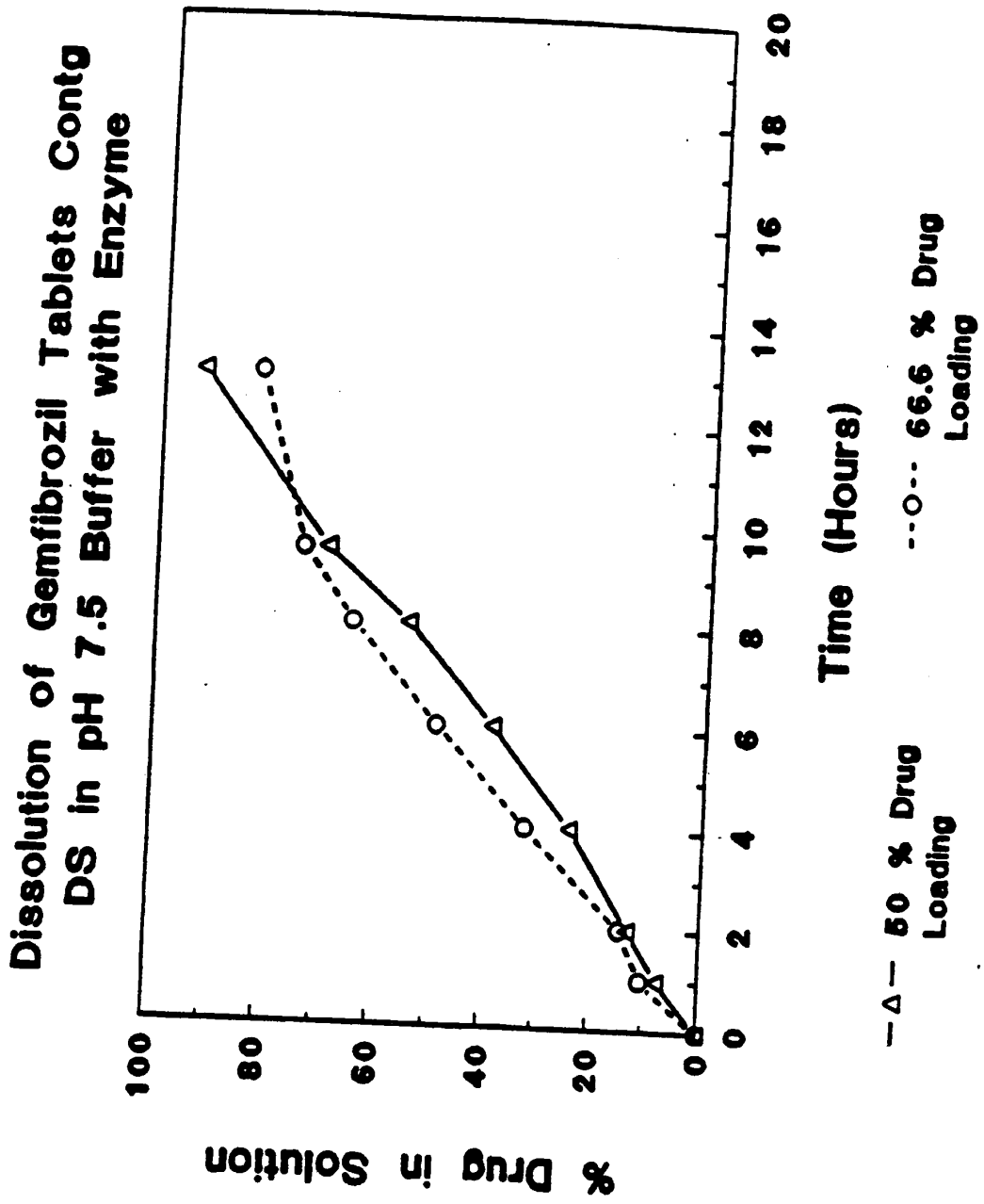
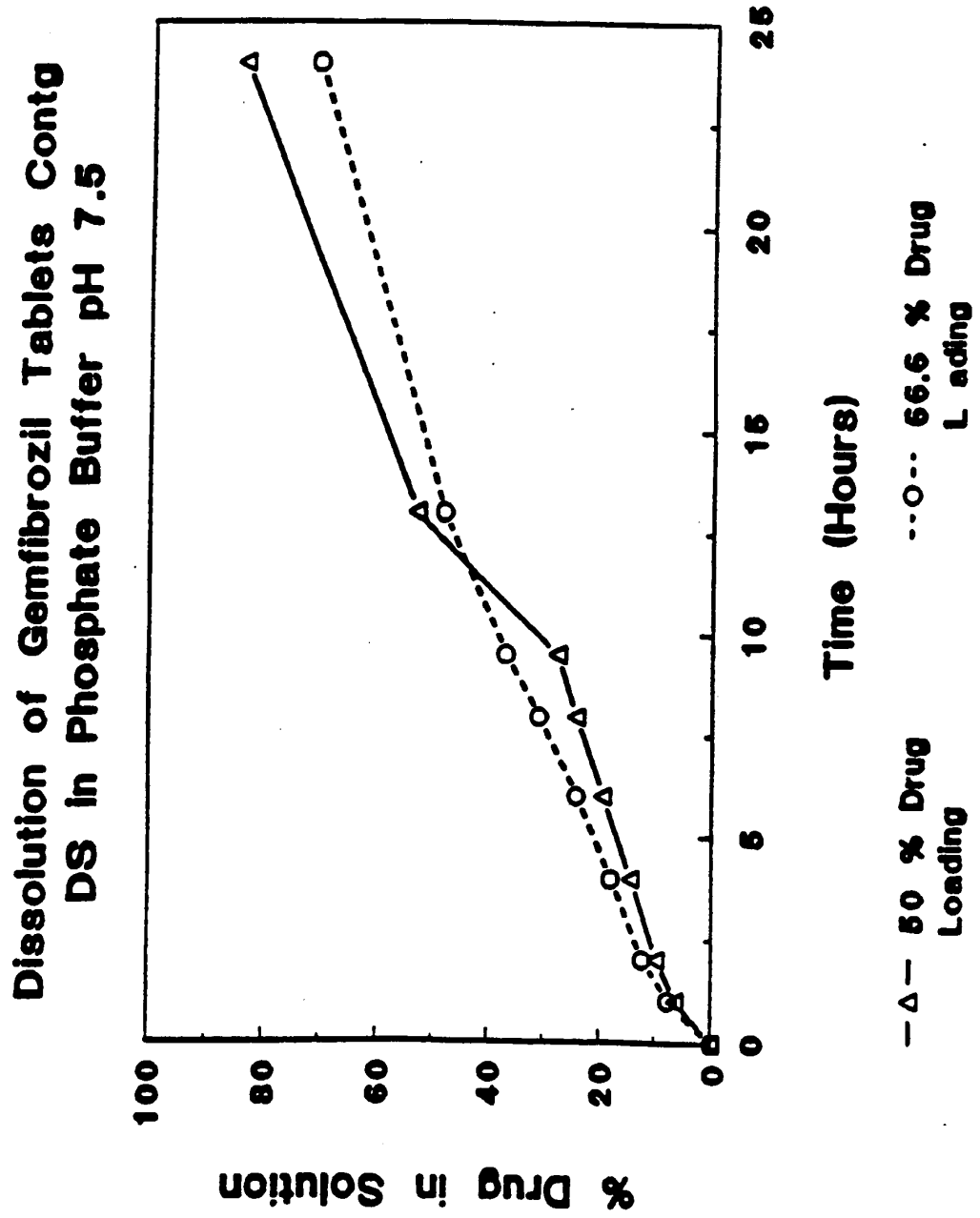

Dissolution of Gemfibrozil Tablets Contg
DS in pH 7.5 Buffer with Enzyme
% Drug in Solution
0
20
40
60
80
100
0
2
4
6
8
10
12
14
16
18
20
Time (Hours)
—△— 50 % Drug Loading
--○-- 66.6 % Drug Loading

FIGURE 23

FIGURE 24


Dissolution of Gemfibrozil Tablets Contg
DS In Phosphate Buffer pH 7.5
% Drug in Solution
0
20
40
60
80
100
0
5
10
15
20
25
Time (Hours)
—Δ— 50 % Drug Loading
--O-- 66.6 % Drug Loading

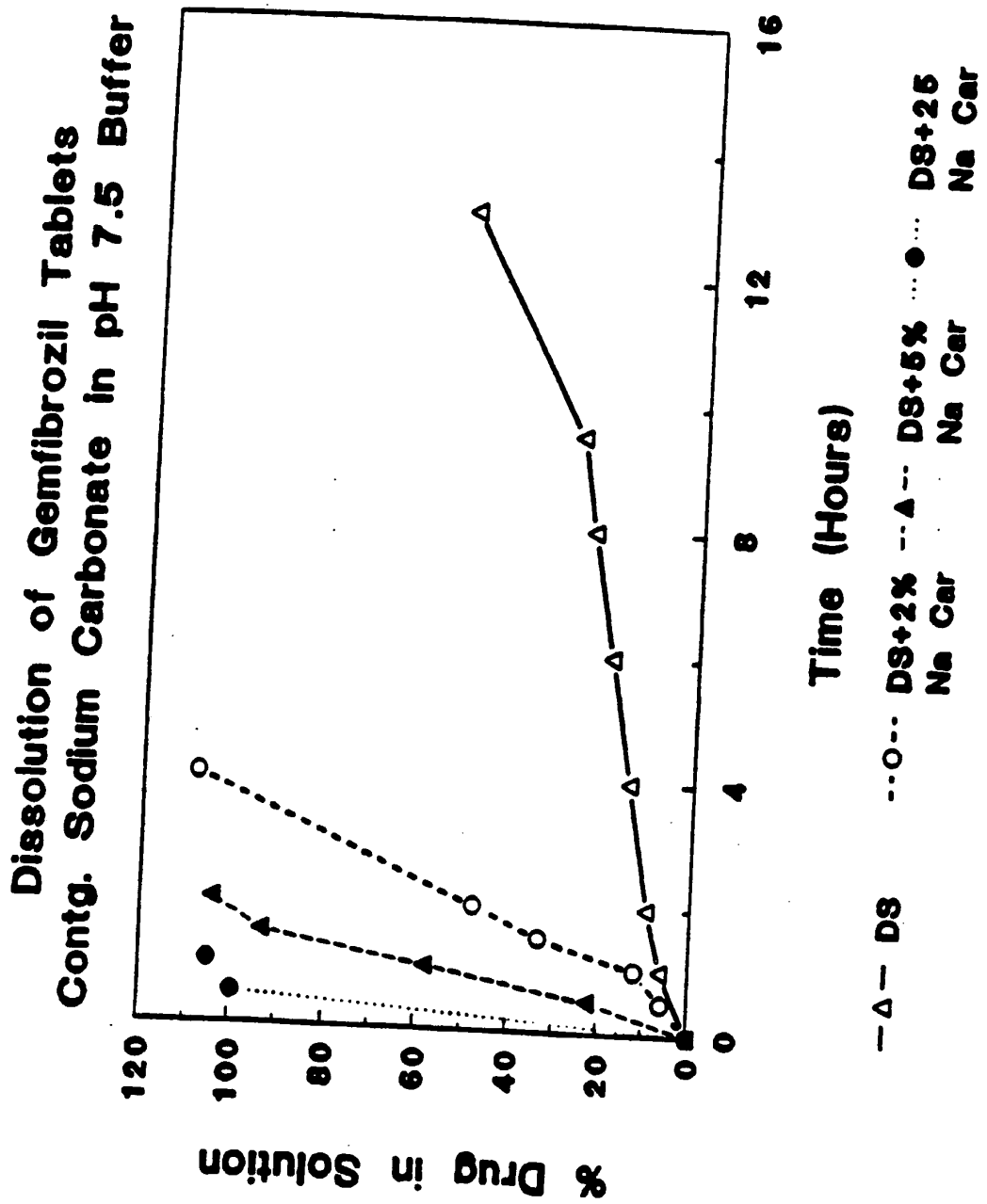

Dissolution of Gemfibrozil Tablets
Contg. Sodium Carbonate in pH 7.5 Buffer
% Drug in Solution
120
100
80
60
40
20
0
0
4
8
12
16
Time (Hours)
—Δ— DS
--o-- DS+2% Na Car
--▲-- DS+5% Na Car
···● DS+25 Na Car

FIGURE 25

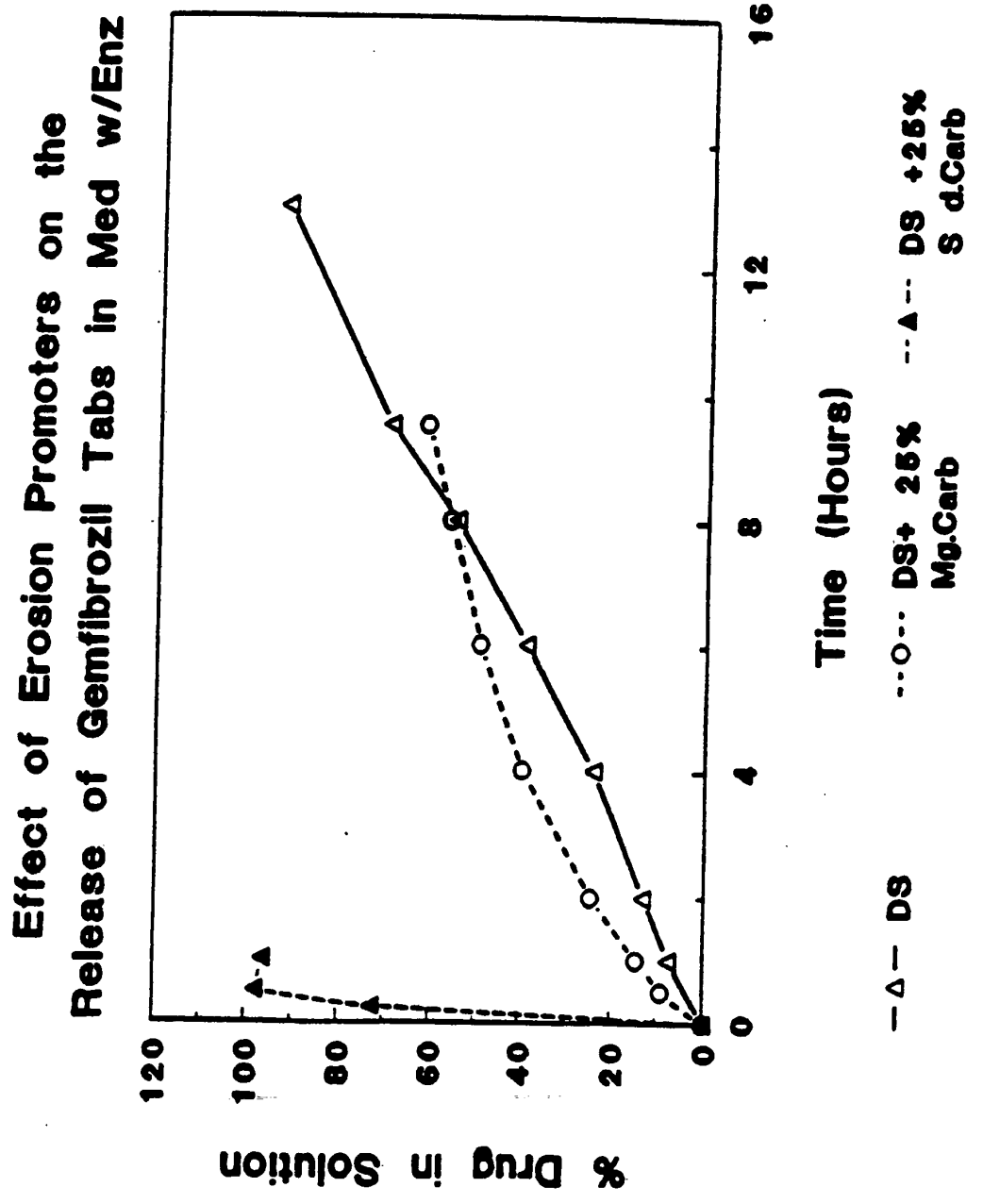

Effect of Erosion Promoters on the Release of Gemfibrozil Tabs in Med w/Enz
% Drug in Solution
120
100
80
60
40
20
0
0
4
8
12
16
Time (Hours)
—△— DS
--○-- DS+ 25% Mg.Carb
--▲-- DS +25% S d.Carb

FIGURE 26

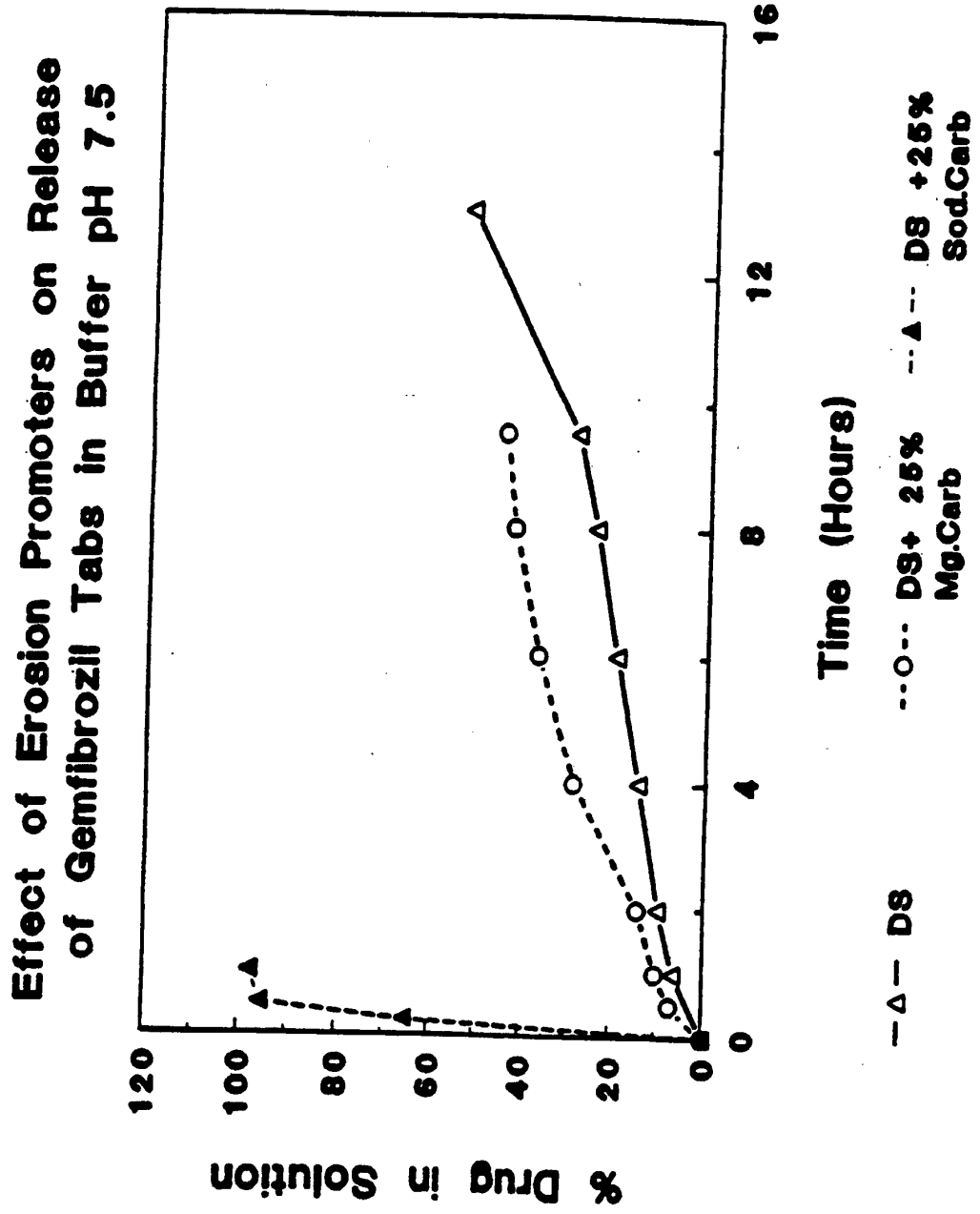

Effect of Erosion Promoters on Release of Gemfibrozil Tabs in Buffer pH 7.5
% Drug in Solution
120
100
80
60
40
20
0
0
4
8
12
16
Time (Hours)
—Δ— DS
--O-- DS+ 25% Mg.Carb
--Δ-- DS +25% Sod.Carb

FIGURE 27

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01762

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/20

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP,A,0118240 (WARNER-LAMBERT) 12 September 1984, see all the claims, in particular claims 11-12 (cited in the application)	1-7,11, 25-31, 34-36
Y	WO,A,9005161 (I. TOMKA) 17 May 1990, see the claims 1,3-4,6-7,13-18,24,29-30,33	1-7,11, 25-31, 34-36
Y	STN Information Services Data Base: Chemical Abstracts, vol. 112, no. 4, (Columbus, Ohio, US), J. HERMAN et al.: "Modified starches as hydrophilic matrixes for controlled oral delivery. I. Production and characterization of thermally modified starches", see abstract no. 25512n, & INT. J. PHARM., 1989, 56(1), 51-63, see the whole abstract (cited in the application)	1-7,11, 25-31, 34-36

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17-06-1992	21.07.92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201762 SA 58245

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/07/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0118240	12-09-84	AU-B- 572119	05-05-88
		AU-A- 2465684	23-08-84
		CA-A- 1238738	28-06-88
		JP-A- 59196335	07-11-84
		US-A- 4673438	16-06-87
		US-A- 4738724	19-04-88
WO-A- 9005161	17-05-90	AU-B- 620934	27-02-92
		AU-A- 4427989	28-05-90
		CA-A- 2001587	03-05-90
		EP-A- 0397819	22-11-90
		JP-T- 3502113	16-05-91